IN THE UNITED STATES PATENT OFFICE

Inventor : W. Roy KNOWLES, M.D.
Filing Date: 19 July 2000
Ser. No.: 09/619,142
Examiner: Vickie KIM
Art Unit: 1614

Honorable Commissioner of Patents
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APPEAL BRIEF

This APPEAL BRIEF is submitted in response to the 20 Feb. 03 OFFICE ACTION and the 22 May 03 PETITION DECISION. pursuant to the accompanying NOTICE OF APPEAL. This is a Special Case because it has undergone more that two OFFICE ACTIONS, and is subject to an approved PETITION TO MAKE SPECIAL.

REAL PARTY IN INTEREST

The real party in interest is Knolltech Pharmaceutical, Inc., a Nevada corporation and the assignee of the entire interest in the patent.

RELATED APPEALS AND INTERFERENCES

A PETITION in this case has been filed with the Court of Appeals for the Federal Circuit.

STATUS OF CLAIMS

Claims 1-5, 7-16 and 18-22 stand five-times rejected.

STATUS OF AMENDMENTS

There are no pending Amendments.

SUMMARY OF INVENTION

Overview

The invention relates to maintaining healthy hair and preventing abnormal hair loss, by using *minoxidil* together with *a skin penetration enhancer* and a *testosterone blocker* or *inhibitor*.

The Art and Its Shortcomings

The background art has been amply explored in the six OFFICE ACTIONS issued in this case.[1]

Minoxidil

Minoxidil in the systemic blood circulation is a potent anti-hypertensive cardiovascular drug. The art of record shows this. *See, e.g.*, Bradbury, U.S. 6,124,362 at col. 1, lines 28-29. Minoxidil over dosage may create cardiac arrhythmia. *E.g.*, GIBSON at col. 2, lines 10-21. Minoxidil is used topically as an anti-alopecia agent (*e.g.*, ROGAINE®). Topical minoxidil is not very effective against hair loss. The art cited by the Examiner uniformly teaches this. *E.g.*, HOKE at col. 3 lines 4-11; BRADBURY at col. 1 lines 31-33; BAZZANO, U.S. 6,183,817 at col. 3 lines 53-56, col. 5 lines 17-42, and col. 4 lines 49-54, 63-65; PARTAIN, U.S. 4,946,870 at col. 13, line 59 to col. 14, line 2.

The Examiner's references also teach that topical use of minoxidil with a skin penetrating agent would load the drug into the systemic blood circulation. *E.g.*, RAJADHYAKSHA, U.S. 5,482,965 at col. 3 line 53-60, col. 7 line 40-57, col. 10 line 11-14,

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[1] This case has an exceptionally well-developed factual record, which includes, *inter alia*, a variety of non-patent references, including W.F. BERGFIELD, Minoxidil Results (Cleveland Clinic Fdn. 1986); V.C. FIEDLER-WEISS, Minoxidil (Dermatologic Clinics, 1987); Kincl, 9 J.Steroid Biochem. 83; Medical Economics Inc., ROGAINE® product insert, PHYSICIANS' DESK REFERENCE (Med. Econ. Inc. 2000); S.A. MIKULAK *et al.*, 50 J. Pharm. Pharmacol 133 (1997); E.A. OLSEN *et al.*, 15 J. Am. Acad. Dermatol. 30 (1986); E.A. OLSEN, 15 J. Am. Acad. Dermatol. 185 (1985); R.A. DE VILLEZ, 121 Arch. Dermatol. 197 (1985); as well as the following U.S. and foreign patents: Bazzano, 6,183,817; Bonte, 5,723,149; Bradbury, 6,124,362; Bromberg, 5,939,485; Buck, 5,609,858; Buck, 5,512,275; Casero, 5,340,579; Catz, WO/93/088__; Chidsey, 4,139,619; Chizick, 5,972,345; Crandall, 6,333,067; Diani, 5,578,599; Gibson, 5,015,470; Grollier, 5,192,534; Hachiman, JP-246836; Hoke, 5,994,319; Kita, 6,162,801; Liao, 5,422,371; Liao, 5,605,929; Lishko, 5,753,263; Messenger, 6,020,327; Mikulak, 50/2 J. Pharm Pharmacol. 153 (1998); Orentreich, 5,053,403; Patel, 4,663,970; Rajadhyaksha, 5,482,955; Roentsch, 5,654,337; Tien, 5,574,011; Wong, 6,824,072; Zupan, 4,440,777.

col. 18 line 1-28, col. 18 line 55 to col. 19 line 12, and Example 32; *see also* KNOWLES, W.R., SUPPLEMENTAL DECLARATION at ¶¶ 7-10 (25 April 2001).[2] The Examiner does not dispute that systemic administration of minoxidil risks precipitating cardiac side effects. OFFICE ACTION (27 Mar. 01). The examiner concedes that such risk is unacceptable for cosmetic use for hair loss. *Id.* Thus, minoxidil sold for hair loss has never included skin penetration enhancer. SPECIFICATION at 2-7; KNOWLES, W.R., RULE 132 DECLARATION at ¶ 7 (5 Feb. 2001); *see* Medical Economics Inc., ROGAINE® topical minoxidil U.S.P. product insert, reprinted in PHYSICIANS' DESK REFERENCE (Med. Econ. Inc. 2000);.

Further, GIBSON notes that certain of these adverse systemic effects have been reported following topical application of minoxidil, apparently without penetration enhancer:

> In spite of the apparent stimulation of hair growth or regrowth reported independently by Bazzano and Chidsey, following topical application of minoxidil or related compounds, there is general concern that systemic side-effects can result, particularly following topical application of minoxidil. Thus it s generally recognized in the medical literature that the side effects of orally administered minoxidil are very serious, and include fluid retention, tachycardia, dyspnea, gynecomastia, fatigue, nausea and cardiotoxicity. There is also evidence that certain side effects have been experienced following topical application of minoxidil.

GIBSON at col. 2, lines 10-21. GIBSON thus teaches that systemically-administered minoxidil poses significant health risks. GIBSON thus teaches that topical minoxidil - even without added penetration enhancer - may precipitate cardiac side effects.

Testosterone Blocker / Inhibitor

Testosterone blockers and inhibitors are known in the art. Progesterone, for example, is a birth control drug. Its systemic side effects include carcinogenicity, decreased libido,

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[2] See also Hoke, United States Letters Patent No. 5,994,319, teaching that progesterone and minoxidil are unacceptable for hair loss (progesterone has severe adverse systemic effects, col. 4 lines 18-23; minoxidil has "potent" cardiovascular side effects and doesn't work well, col. 3 lines 4-14); Hoke instead advocates and claims anti-sense nucleotides. Bradbury, United States Letters Patent No. 6,124,362, teaches the cosmetic use of lupine triperpine compounds for hair-growth. Bradbury notes that minoxidil is "a potent antihypertensive," and that "not all people respond to minoxidil and the efficacy level is limited in those individuals who do." Col. 1, lines 25-34.

feminization, and impotency. HOKE at col. 4 line 22-24. It also "systemically disrupts the menstrual cycle in women." ORENTREICH, U.S. 5,053,403 at col. 7. The Examiner concedes that these adverse side effects are "well documented." OFFICE ACTION at 5 (24 Oct. 2000).

Progesterone has been disclosed topically for hair loss. ORENTREICH, U.S. 5,053,403 at 7. Such teaching, however, acknowledges concerns over potentially dangerous side effects, due to progesterone leaching into the systemic circulation. The art thus teaches away from including skin penetration enhancer with progesterone. Id. at col. 1 lines 45-52. Similarly, finasteride ("an effective inhibitor of the enzyme 5α-reductase") is known in the art to not be appropriate for use with penetration enhancer. HOKE at col. 4 line 18-24, col. 5 line 4-6.

The foregoing is expressly taught by the Examiner's own references, and is undisputed by the Examiner. *See* OFFICE ACTION at ¶ 1 (9 May 2002) (withdrawing rejections over HOKE, ORENTREICH, BRADBURY, BAZZANO, RAJADHYAKSHA).

Dr. Knowles' Counter-Intuitive Solution

Dr. Knowles has turned this conventional wisdom on its head. He has found that, contrary to the teachings of the art, penetration enhancer can safely be used with minoxidil and a testosterone blocker or inhibitor - **if** used properly. SPECIFICATION at 8-9. He tested his invention in rigorous, confidential clinical trials. His invention has been proven **ten times more effective** over prior art preparations, with **qualitatively better results**, with none of the **adverse side effects** feared in the prior art. SPECIFICATION at 8, 12-14; Knowles, W.R., RULE 131 DECLARATION (5 Feb. 2001) Knowles, W.R., RULE 132 DECLARATION (5 Feb. 2001).

The claims are drawn to a combination of minoxidil and a 5α-reductase inhibitor[3] and a skin-penetration enhancer. Claims 1, 3 and 4 read (emphasis added):

1. A composition of matter intended for topical use in preventing or treating alopecia, or maintaining healthy hair, said composition of matter comprising:

[3] The Examiner prefers to use the term "5α-reductase inhibitor" as a substitute for Applicant's term "testosterone blocker." *E.g.*, OFFICE ACTION at 7 (28 Sept. 2001). Applicant has amended the claims accordingly. AMENDMENT pg. 2, lines 14-19 (10 Jan. 2002).

a) an active compound selected from the group consisting of: a pharmaceutically or cosmetically effective topical amount of a 5α-reductase inhibitor and minoxidil, and

b) a non-retinoid penetration enhancer, said penetration enhancer present *in a concentration sufficient to aid said active compound in penetrating the skin surface to a depth of approximately the depth of hair bulbs.*

3. The composition of claim 1, wherein said active compound comprises minoxidil.

4. The composition of claim 3, further comprising a 5α-reductase inhibitor.

Claim 4 thus requires minoxidil + 5α-reductase inhibitor + penetration enhancer.

Conclusion

The examiner concedes that the aforementioned references lack certain claim limitations. The examiner, however, now relies on new references. The examiner concedes, however, that the same claim limitations are lacking in the new references as well. Further, Applicant has sworn behind the newly raised rejections.

Because the examiner concedes that the new references lack these claim limitations, and because the Applicant has sworn behind the new references, the rejections *must* be withdrawn as a matter of law.

Issues Presented

Whether the examiner is collaterally estopped from further contesting the issue of whether the claims can be anticipated by a reference which does not teach "penetration to a depth of approximately the depth of hair bulbs"?

References

The following references are enclosed (handwritten notations on the references are believed to be the examiner's):

BAZZANO

BAZZANO, United States Letters Patent No. 5,183,817, claims using retinoid compounds for hair growth. BAZZANO says that minoxidil *does not work* for hair loss. BAZZANO also fails to teach skin penetration enhancer. Significantly, the Examiner has previously agreed with this, and conceded that BAZZANO does not anticipate nor render

obvious the claims. The Examiner thus withdrew all rejections based on BAZZANO. *See* OFFICE ACTION at 3 (9 May 02) (withdrawing all rejections based on BAZZANO).

GIBSON

GIBSON, United States Letters Patent No. 5,015,470, teaches an approach to treating hair loss, entailing using mixtures of hundreds of potential compounds, to inhibit enzymes which interfere with hair growth.

GROLLIER

GROLLIER, United States Letters Patent No. 5,192,534, teaches a "composition for inducing and stimulating hair growth or retarding its loss, based on pyrimidine derivatives and sunscreens."

SCHOSTAREZ

SCHOSTAREZ, United States Letters Patent No. 5,373,012, teaches 5-fluoro substituted minoxidil. SCHOSTAREZ quantifies the cardiac side-effects of each compound, showing that they have similar dose-dependent effects on mean arterial pressure, Fig. 1, and on changes in heart rate, Fig. 2. SCHOSTAREZ further shows that 5-fluoro substituted minoxidil penetrates completely through the skin and into the systemic blood circulation over three times more quickly than plain minoxidil, *see* SCHOSTAREZ at Table IV - creating three times the incidence of adverse systemic side effects.

ZUPAN

ZUPAN, United States Letters Patent No. 4,440,777, teaches eucalyptol as an improved skin penetration enhancer.

Separately-Patentable Claims

The claims are each separately patentable as explained in detail in the following Argument.

ARGUMENT

Section 112 Objection & Rejection

The New Matter Objection Must Be Withdrawn As A Matter Of Law

Paper No. 20 is objected to for introducing "new matter." Applicant respectfully traverses, because the Examiner fails to even bother to say what part of Paper No. 20 allegedly is new matter.[4] The objection thus fails to comply with MPEP § 706.03(o).

Second, the Examiner is required to have objected to this "new matter" in her first responsive Office Action. *See* MPEP § 707.07(g) ("Piecemeal examination should be avoided."); *cf.* MPEP § 602.03 ("In the *first* Office action the examiner *must* point out *every* deficiency"); Here, the Examiner accepted Paper No. 20 without reservation *last year*. Having already accepted Paper No. 20, the Examiner is respectfully believed estopped from now conjuring up alleged new grounds to object.

Applicant assumes the "new matter" is the amendment changing the claim nomenclature to "a non-retinoid penetration enhancer." This amendment adds a negative limitation to the claims. Negative limitations are specifically permitted where the Examiner fails to propose more clear verbiage. M.P.E.P. § 707.07(g) (2001) says, "Certain technical rejections (e.g. negative limitations, indefiniteness) *should not be made* where the Examiner, recognizing the limitations of the English language, is not aware of *an improved mode of definition*" (emphasis added). Here, the Examiner does not propose any "improved mode of definition." The objection should thus be withdrawn.

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[4] The Examiner must specify exactly what part of Paper No. 20 is objectionable. *See* MPEP § 706.03(o) (2001). Form Paragraph ¶ 7.28 requires the Examiner to identify exactly what added material is not supported by the disclosure; the form paragraph reads, "no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: **[2]**."

The Section 112 First Paragraph Rejection Must Be Withdrawn As A Matter Of Law

All pending claims stand rejected under 35 U.S.C. § 112, first paragraph, because the claim limitation "a non-retinoid penetration enhancer" is allegedly not supported by the original disclosure. Applicant respectfully traverses, because the Examiner has failed to plead a *prima facie* case.

As the ***only*** basis for the rejection, the OFFICE ACTION says, "applicant cannot exclude the subject matter that is not considered as the applicant's invention at the time of application filed." OFFICE ACTION at 3 (11 Feb. 2002).

Applicant disagrees. Excluding subject matter not considered the applicant's invention is one of the main reasons to have patent claims - ***that's what patent claims are for!*** In so doing, claims can exclude subject matter by reciting negative limitations.

For example, in In re Wakefield, 422 F.2d 897, 904 (C.C.P.A. 1970), the Examiner (like the Examiner in the immediate case) rejected "the use of a negative limitation excluding the characteristics of the prior art products." The C.C.P.A. reversed the Board. The C.C.P.A. explicitly held that negative claim limitations can be used to "exclude the characteristics of prior art products." Similarly, In re Barr, 444 F.2d. 588, 595 (C.C.P.A. 1971), the Board rejected a negative claim limitation, and the C.C.P.A. reversed the Board. The Court held that negative claim limitations are entirely proper as long as "the boundaries of the patent protection sought are set forth definitely, albeit negatively."

In the immediate case, the OFFICE ACTION does not allege that the negative claim limitation is "indefinite." Because the claims are not even alleged to be indefinite, the rejection must be withdrawn as a matter of law.[5]

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[5] The Examiner appears unaware that acceptable claim nomenclature is not limited to the nomenclature recited in the application as filed. If the Examiner believes the claim nomenclature as amended is ambiguous when interpreted in light of the specification, then the Examiner should simply ask Applicant to "make appropriate amendment to the specification whenever this nomenclature is departed from by amendment to the claims[,] so as to have clear support or antecedent basis in the specification for new terms appearing in the claims." M.P.E.P. § 608.01(o) (2001). This helps the general public more readily understand the claim verbiage.

Prior Art Rejections

BAZZANO Does Not Anticipate Claims 1-4 And 12-15

Claims 1-4 and 12-15 stand rejected as anticipated by BAZZANO. BAZZANO cannot anticipate the claims as a matter of law, because BAZZANO fails to teach *every limitation* of the claims, and fails to *enable practicing* the claimed invention. Significantly, the Examiner has already conceded this on the record, and withdrew all rejections based on BAZZANO. *See* OFFICE ACTION at 3 (9 May 2002).

BAZZANO Does not Enable The Claimed Invention

BAZZANO, United States Letters Patent No. 5,183,817, claims retinoid compounds combined with minoxidil for hair growth. In contrast to her claimed retinoids, BAZZANO says that minoxidil *does not work* for hair loss. BAZZANO at col. 3, line 53-56 and col. 4, lines 49-54. BAZZANO teaches that systemic minoxidil presents serious cardiac side effect risks. Id. at col. 3 line 49-52; col. line 43-45. BAZZANO thus teaches away from using Applicant's claimed combinations, and teaches using her own claimed retinoids instead.

BAZZANO actively teaches away from the claimed invention. BAZZANO says that without added retinoid, *minoxidil does not work.* BAZZANO says:

> Minoxidil is recognized as being somewhat effective in producing new vellus hair growth and sparse terminal hair growth in a pre-selected group of subjects. However, its effect is far from satisfactory in most subjects. * * * minoxidil may not be able to sustain the growth of terminal hairs from the vellus hairs on the scalp. In the majority of subjects with alopecia, terminal hair growth on the scalp may not be initiated or sustained by the topical application of minoxidil nor by its systemic administration.

Id. at col. 3, line 53-56; col. 4, line 49-54. BAZZANO says that without her claimed retinoid compounds, minoxidil lacks any "profound effect" and "cannot" produce a strong response. Id. at col. 5, lines 17 - 42. BAZZANO explains that her claimed retinoids "can initiate cell growth and differentiation (not initiated by minoxidil)" required for hair growth. Id. BAZZANO says minoxidil alone "does not appear to be a sufficient stimulus for hair growth, particularly in an area affected by alopecia." Id. at col. 4, line 63-65. Thus, BAZZANO teaches away from the claimed combinations, which do not require retinoid at all.

BAZZANO Does Not Teach Penetration Enhancer

BAZZANO does not teach skin penetration enhancer. The Examiner has already admitted this, but quipped that penetration enhancer "is not considered to be critical." OFFICE ACTION at 5 (Oct. 24, 2000). The Examiner similarly conceded that while the prior art teaches "delivery vehicles such as ethanol and propylene glycol," "Applicant's claims differ because they require a penetration enhancer." OFFICE ACTION at 8 (28 Sept. 2001). The Examiner has already conceded this, and conceded that BAZZANO fails to anticipate the claims. OFFICE ACTION at 3 (9 May 2002).

The Examiner cannot simply ignore this claim limitation. Because BAZZANO does not disclose this claim limitation, BAZZANO cannot anticipate it as a matter of law. Akzo N.V. v. U.S. Intern. Trade Comm'n., 808 F.2d 1471 (Fed.Cir. 1986), *cert. denied*, 482 U.S. 909.

The Examiner Refuses To Provide Legally-Required Factual Discovery

In response, the Examiner now attempts to contradict her earlier factual findings. First, the Examiner makes a factual assertion that the inert propylene glycol-ethanol vehicle in BAZZANO "has penetration enhancing activity wherein these agents are naturally potentiating the ability of said active agents." OFFICE ACTION at 5 (11 Feb. 2003). This unsupported factual assertion is contradicted by the record. BAZZANO herself calls PEG-ethanol an inert "vehicle." BAZZANO at claim 24; *see also* Knowles, W.R., SUPPLEMENTAL DECLARATION at 1 (25 April 2001); MIKULAK *et al.*, "Transdermal Delivery and Accumulation...," 50/2 J. PHARM. PHARMACOL. 153 (1998) (PEG-ethanol used as inert experimental control); SPECIFICATION at pg. 17, line 15-17, pg. 18, line 16 to pg. 19 line 9; 21 C.F.R. 352.70 (Food & Drug Administration treats PEG as an inert vehicle); *see* ROGAINE® brand topical minoxidil F.D.A.-approved product insert (PEG-ethanol used as an inert vehicle).

Responding to Examiner's unsupported factual assertion that PEG-ethanol is "notoriously known as a penetration enhancer," OFFICE ACTION at 4 (28 Sept. 2001), Applicant requested the Examiner make of record an AFFIDAVIT OF REFERENCES supporting

this assertion. *See* RESPONSE at pg. 9 (8 Feb. 2001). The Examiner has refused to respond. Because the Examiner refuses to produce an AFFIDAVIT OF REFERENCES, the Examiner's erroneous factual assumption must be withdrawn - along with the rejection based on it. Ex parte Nouel, 158 USPQ 237 (B.P.A.I. 1967) (relying on judicial notice for a fact invalidating a claim is reversible error); Ex parte Grochowski, No. 95-1343 at 5 (B.P.A.I., June 27, 1995); In re Ahlert, 165 USPQ 418, 420 (C.C.P.A. 1970); In re Eynde, 178 USPQ 470, 474 (C.C.P.A. 1973).

The Examiner also changed position to say that, contradicting the Examiner's own previous factual assertions, BAZZANO's retinoid is itself a penetration enhancer. OFFICE ACTION at 8 (28 Sept. 2001). The Examiner is respectfully believed estopped from contradicting her earlier factual findings. *See* Overland Motor Co. v. Packard Motor Co., 274 U.S. 417, 421 (1927) ("Especially is this [collateral estoppel] principle applicable to the proceedings of the Patent Office, which are so nearly akin to judicial proceedings as to be most appropriately designated as quasi-judicial."); Allen v. McCurry, 449 U.S. 90, 94 (1980) (Examiner cannot re-litigate any issue that was raised or that "*could have been* raised" previously); Schwartz, S.D., *Res Judicata As Applied in Patent Office Prosecution...*, 159 J. PAT. OFF. SOC. 637, 638 (1967) (in Patent Office proceedings, collateral estoppel is "*an absolute bar*" to relitigation).

Applicant has also filed an amendment to expressly clarify that the claim term "penetration enhancer" does not include BAZZANO's retinoid compounds.

BAZZANO Combined With GROLLIER
Does Not Render Claims 11 And 22 Obvious

Grollier teaches a composition for inducing and stimulating hair growth or retarding its loss, based on pyrimidine derivatives and sunscreens. Id. at Title. GROLLIER does not rectify the aforementioned shortcomings of BAZZANO; the 20 Feb. 03 OFFICE ACTION does not allege otherwise. Thus, the combination of BAZZANO + GROLLIER suffers from the same shortcomings as does BAZZANO alone.

GIBSON Does Not Anticipate
Claims 1, 3, 12, 14

Claims 1, 3, 12, and 14 stand rejected as anticipated under 35 U.S.C. § 102(b) by GIBSON *et al.* Applicant respectfully traverses.

GIBSON Addresses Hair Growth Enzymes

GIBSON says that, in contrast to the art of record, he has "now identified chemical inhibitors of key enzymes and other cellular events involved respectively in the breakdown of proteoglycan or glycosaminoglycan chains, and in blocking of cellular uptake of intact glycosaminoglycan chains." Id. at col. 4, lines 1-5. GIBSON thus proposes addressing hair loss by using one or more "chemical inhibitors" of various enzymes involved in hair growth. Id. GIBSON summarizes, "since there is already evidence for a link between the presence of intact glycosaminoglycans and hair growth, we have suggested that prevention of proteoglycan and glycosaminoglycan breakdown may lead to earlier onset and/or prolongation of anagen [hair growth phase]. This would effectively retard hair loss and reverse baldness." Id. at col. 3, lines 38-45.

GIBSON Validates His Rat Model
With Commercially-Available
ROGAINE® Topical Minoxidil

To measure the effectiveness of certain of his enzyme-inhibiting combinations, GIBSON uses laboratory rats. As a preliminary matter, to make sure that rats will respond to human hair growth preparations, GIBSON first "validates" his rat model, or confirms whether or not rats do in fact respond to known hair growth preparations. GIBSON does this by testing rats' responsiveness to commercially-available minoxidil. GIBSON says, "Validation of rat model for hair growth using Minoxidil. The rat model was validated by showing that topical application of a known promoter of human hair regrowth, namely 2% (w/v) minoxidil in a vehicle cf 70% ethanol, 20% water and 10% propylene glycol, caused a

significant increase of 55% in hair growth as shown" in Table 1. Id. at col. 20, lines 9-26. GIBSON's Table 1 thus teaches that ROGAINE® brand minoxidil works on rats.[6]

GIBSON Teaches Away From
The Claimed Combinations

GIBSON confirms the teachings of the art that minoxidil does not in fact work well. GIBSON finds that minoxidil alone increases hair growth only 9% over inert vehicle alone. Id. at col. 20, line 59 *et seq.* In so doing, GIBSON confirms the consistent teachings of the numerous other references of record.

GIBSON also explores the reason for minoxidil's lack of effectiveness. GIBSON measures minoxidil's effect on the hair growth enzyme β-glycosaminoglycan. Id. at col. 23, lines 54 *et seq.* GIBSON concludes, "minoxidil is a weak enzyme inhibitor." Id. at col. 24, line 10. GIBSON thus reasons that because minoxidil alone does not work well, it must be combined with "a second chemical inhibitor and/or an activity enhancer." Id. at lines 14-15.

GIBSON confirms that systemically-administered minoxidil poses significant health risks. *See supra.* To minimize these adverse systemic effects, GIBSON teaches combining minoxidil with a variety of other compounds which GIBSON says are effective in regulating hair growth. GIBSON specifically prefers mixing minoxidil with any of several dozen hair-growth enzyme affecting compounds including, *e.g.*, zinc gluconate; magnesium sulphate; D-glucaro-1,4-lactone; 1,10-phenanthroline; D-glucosamine-3-sulphate; L-idaro-1,4-lactone; L-galactano-1,4-lactone; *et cetera.* Id. at col. 10, lines 39-60 and col. 18, lines 55 *et seq.* GIBSON specifically describes the synergistic combination of minoxidil with one of these compounds, D-glucaro-1,4-lactone. Id. at col. 20, lines 59 *et seq.* GIBSON says that such synergistic combinations are advantageous because they allow "a lower than usual

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[6] Note that the composition used in TABLE 1 is simply commercially-available ROGAINE®. It does not include skin penetration enhancer. GIBSON himself says the ethanol (ethyl alcohol) which he used in Table 1 is "solvent" rather than penetration enhancer. Id. at col. 11, line 53. GIBSON also uses propylene glycol. GIBSON does not expressly describe propylene glycol as "solvent" nor "penetration enhancer," but THE MERCK INDEX notes that propylene glycol is a "substitute for ethylene glycol," THE MERCK INDEX at ¶ 7947 (13th ed. 2001). Ethylene glycol is described by GIBSON as a "solvent." Id. at col. 11, line 53.

The OFFICE ACTION, however, says that Table 1 anticipates the claims. It doesn't. Table 1 does not show the claimed invention. Table 1 shows neither "penetration enhancer" nor "penetration to a depth approximately of hair bulbs." Significantly, the OFFICE ACTION fails to even allege that Table 1 shows these claim limitations. Because the OFFICE ACTION fails to even allege Table 1 teaches "penetration enhancer" nor "depth of hair bulbs," Table 1 cannot anticipate as a matter of law.

concentration of minoxidil" to be used, with an "enhanced in-use safety margin, bearing in mind possible contra-indications which allegedly follow topical application of higher concentrations of minoxidil." Id. at col. 21, lines 27-31. GIBSON thus confirms the systemic dangers of minoxidil, and teaches minimizing these dangers by minimizing the minoxidil used, using instead other compounds which interfere with hair-growth regulatory enzymes.

GIBSON Fails To Enable
The Claimed Invention

GIBSON also says that minoxidil can be mixed with "certain penetration enhancers and certain cationic polymers." Id. at col. 11, lines 1-2. GIBSON then lists several thousand examples of what he calls "penetration enhancers." Id. at col. 14, line 16 to col. 18, line 39. A cursory review of GIBSON's list shows that it includes many compounds not generally recognized in pharmacology as safe nor effective skin penetration enhancers; these compounds include, *inter alia*, carcinogenic, teratogenic and caustic agents like paint remover solvent,[7] gasoline octane booster,[8] ethanol denaturant,[9] polyurethane manufacturing intermediate,[10] gasoline additive,[11] varnish drier,[12] insecticide,[13] nail polish remover,[14] dioxane, and solvent for polyvinyl chloride.[15]

GIBSON teaches that one or more of these compounds may in turn be mixed with a universe of several thousand compounds which may interfere with baldness-related enzymes. These compounds include, for example, soluble metal anions,[16] ammonium salt anions,[17] aldolactones,[18] esterified aldolactones,[19] monosaccharides,[20] esterified monosaccharides,[21]

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[7] 2-methyl propan-2-ol.
[8] 2-methyl propan-2-ol.
[9] 2-methyl propan-2-ol.
[10] hexan-2,5-diol.
[11] pentan-2,4-diol.
[12] pentan-2,4-diol.
[13] pentan-2,4-diol.
[14] Acetone.
[15] Tetrahydrofuran.
[16] id. at col. 7, lines 39-59.
[17] id. at col. 7, lines 39-59.
[18] id. at col. 7, line 67 et seq.
[19] Id.
[20] id. at col. 8, lines 55 *et seq*.

piperidines,[22] glycosaminoglycan chain cellular uptake inhibitors,[23] phenol,[24] red pepper tincture,[25] estradiol,[26] resorcinol,[27] peppermint oil,[28] - and minoxidil.[29]

GIBSON therefore suggests that one or more of the several thousand compounds he classifies as "penetration enhancers" can be combined with one or more of the several thousand compounds which could interfere with baldness-related enzymes. Selecting one compound from each of these two groups makes millions of potential combinations. Varying the amounts of each of the two ingredients selected makes even more potential combinations. Discerning which one (if any) of these millions of possible combinations would make the claimed invention, would take years of research. *See* Knowles, W.R., RULE 132 DECLARATION at ¶¶ 8-9 (5 Feb. 2001).

This is "undue experimentation." The Federal Circuit recently said that even with far fewer potential combinations, the reference must "single out particular" combinations, to enable them:

> It is an old custom in the woods to mark trails by making blaze marks on trees. It is of no help in finding a trail or in finding one's way through the woods . . . to be confronted simply by a large number of unmarked trees. We are looking for blaze marks which single out particular trees. We see none.

Purdue Pharma L.P. v. Faulding Inc., *slip op.* (Fed.Cir. 25 Oct. 2000). The Federal Circuit further cautions, "the blaze marks directing the skilled artisan to that tree must be in the originally filed disclosure." Id.

Here, GIBSON has no "blaze marks" singling out or directing the skilled artisan through the millions of possible combinations, to Applicant's specific claimed invention. The OFFICE ACTION does not allege otherwise. GIBSON fails to expressly say which "penetration enhancer" should be combined with minoxidil, nor how much of the penetration

---

[21] Id.
[22] id. at col. 9, lines 22 *et seq.*
[23] Col. 9, lines 60 *et seq.*
[24] id. at col. 12, lines 39-64.
[25] Id.
[26] Id.
[27] Id.
[28] Id.
[29] Id. at col. 9, lines 45-49.

enhancer should be used, nor how much minoxidil should be used, to create a composition to penetrate to a depth of the hair bulbs. The OFFICE ACTION does not allege otherwise. Because GIBSON requires undue experimentation, it cannot anticipate. Id.; *accord*, Biogen, Inc. v. Amgen, Inc., 973 F.Supp 39, 43 (D.Mass. 1997).

GIBSON Cannot Anticipate Because
GIBSON Does Not Enable "Penetration
To A Depth Of The Hair Bulbs"

GIBSON cannot anticipate because it does not enable each claim limitation.

To anticipate, the reference must enable the claimed invention, including all claim limitations, with sufficient clarity and detail to establish that the subject matter already existed in the prior art. Elan Pharmaceuticals, Inc. v. Mayo Fdn. For Med. Educ. & Rsch., 304 F.3d 1221, 1227-28 (Fed. Cir. 2002); Biogen, Inc. v. Amgen, Inc., 973 F.Supp 39, 43 (D.Mass. 1997). To enable, the reference must provide more than a mere "precatory suggestion" to pursue the claimed invention; the reference must explain how to practice the claimed invention. The Federal Circuit notes,

> On the law of anticipation, precedent has not improved on the words of Judge Learned Hand: "No doctrine of patent law is better established than that a prior patent or other publication to be an anticipation must bear within its four corners adequate directions for the practice of the patent invalidated. If the earlier patent offers no more than a starting point for further experiments, if its teaching will sometimes succeed and sometimes fail, if it does not inform the art without more how to practice the new invention, it has not correspondingly enriched the store of common knowledge, and is not anticipation."

Id. at 1229, *quoting* Dewey & Almy Chem. Co. v. Mimex Co., 124 F.2d 986, 989 (2nd Cir. 1942) (Hand, J.). Thus, a "precatory suggestion of general procedures that may or may not succeed" fails to enable - and thus fails to anticipate. Id. at 1230.

Here, GIBSON describes millions of potential combinations. These millions of potential combinations are the "starting point for [millions of] further experiments." These experiments "will sometimes succeed and sometimes fail" to create the claimed invention. GIBSON fails to expressly say which "penetration enhancer" should be combined with minoxidil, nor how much of the penetration enhancer should be used, nor how much minoxidil should be used, to create a composition to penetrate to a depth of the hair bulbs.

The OFFICE ACTION does not allege otherwise. GIBSON therefore fails to inform the art how to practice the claimed invention.

It may be argued (albeit the OFFICE ACTION does not) that while this knowledge is not expressly taught in GIBSON, it is inherent in GIBSON. This argument fails, because no facts of record show that the claim limitations are necessarily present in GIBSON.

When anticipation is based on inherency of *limitations not expressly disclosed* in the assertedly anticipating reference, it must be shown that the undisclosed information was known to be present in the subject matter of the reference. Elan Pharmaceuticals, 304 F.3d at 1228. "An inherent limitation is one that is necessarily present; invalidation based on inherency is not established by 'probabilities or possibilities.'" Id. In the immediate case, some of GIBSON's millions of potential combinations might possibly, or even probably, contain every limitation of the pending claims. Such "probabilities or possibilities," however, fail to anticipate the claims as a matter of law. Id.

It may be argued that one of skill in the art would know how to experiment with GIBSON to sift from the myriad possible combinations, the ones which anticipate the claims. This argument fails, because GIBSON's shortcomings cannot be rehabilitated by recourse to the skill in the art. This is because "It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement." Biogen, 973 F.Supp. at 45. Accordingly, GIBSON must bear "*within its four corners*" adequate directions for the practice of the claimed invention. *See* Elan Pharmaceuticals, 304 F.3d at 1229. GIBSON fails to expressly say which "penetration enhancer" should be combined with minoxidil, nor how much of the penetration enhancer should be used, nor how much minoxidil should be used, to create a composition to penetrate to a depth of the hair bulbs. The OFFICE ACTION does not allege otherwise. GIBSON's specification fails to supply the novel aspects of the claimed invention. GIBSON therefore fails to enable.

GIBSON Combined With BAZZANO Does Not Render Obvious Claims 2, 4-5, 7-10, 13, 15-16 And 18-21

The OFFICE ACTION fails to state a *prima facie* case that the claims are obvious over the combination of GIBSON + BAZZANO.

As a preliminary matter, contrary to the OFFICE ACTION'S assertion, BAZZANO does not teach combining 5α-reductase inhibitor with minoxidil, but with a retinoid. The OFFICE ACTION does not allege that the combination of 5α-reductase inhibitor + retinoid anticipates any claim.

The OFFICE ACTION says one would be motivated to make this combination for two reasons: the combination has two components "utilizing different biological pathway and potentiating other component's activity." OFFICE ACTION at 7 (20 Feb. 03).

No evidence of record in the prior art shows the two components "utilize different biological pathway." This factual assertion *has no basis at all* in the rather voluminous evidence of record in this case.[30] Because this factual assertion has no evidentiary basis, it must be withdrawn as a matter of law.

Similarly, no evidence of record shows either component "potentiates" the other component's activity. This factual assertion is baseless. It must therefore be withdrawn.

The only "motivation to combine" alleged is therefore tow baseless factual assertions which must be withdrawn, along with the rejection based on them.

GIBSON Combined With SCHOSTAREZ Does Not Render Obvious Claims 2, 4-5, 7-10, 13, 15-16 And 18-21

The claims stand rejected as obvious over GIBSON combined with SCHOSTAREZ. This rejection should be withdrawn, because SCHOSTAREZ expressly teaches away from making the claimed combination.

SCHOSTAREZ teaches 5-fluoro substituted minoxidil. SCHOSTAREZ shows that 5-fluoro minoxidil has dose-dependent cardiac effects similar to that of minoxidil. For

---

[30] It is also somewhat amusing. The Examiner previously asserted that one would be motivated to combine progesterone with antisense oligonucleotides because they "have same biological pathway (working via same mechanism)." OFFICE ACTION at 5 (24 Oct. 2000). When Applicant pointed out that this factual assertion is baseless and baldly incorrect, the Examiner withdrew it.

example, SCHOSTAREZ Fig. 1 shows that 1.5 mg/kg of 5-fluoro minoxidil and of minoxidil have similar effects on mean arterial pressure. SCHOSTAREZ Fig. 2 shows that 1.5 mg/kg of 5-fluoro minoxidil and of minoxidil have similar effects on changes in heart rate, both compounds precipitating sharp increases in heart rate immediately after dosing and persisting for at least seventy-two hours after dosing. SCHOSTAREZ aptly summarizes the powerful cardiac effects of both compounds:

> The Formula I compounds are used for the treatment of cardiovascular disorders wherever a potent hypotensive drug is indicated. The compounds and compositions of Formula I are administered in a therapeutic effective amount which is an amount sufficient to control hypertension, congestive heart failure, angina and peripheral vascular disorders in the host being treated such as mammals which includes humans. Typically, the Formula I compounds are used in unit dosages of from 0.01 to 300 mg in oral or injectable preparations. Preferably, the Formula I compounds are used in unit dosages of 0.001 to 10 mg/kg for administration by routes either oral, sublingual, transdermal, or parenteral such as subcutaneous, intramuscular, or intravenous injection.
>
> The particular dose of compound administered according to this invention will of course be determined by the particular circumstances surrounding the case, including the compound administered, the particular cardiovascular disorder being treated, and similar considerations.

Id. at col. 7, lines 11-32.

In addition to the compounds' "potent hypotensive drug" effect, SCHOSTAREZ shows that unlike conventional minoxidil, 5-flouro substituted minoxidil rapidly penetrates through the skin and into the systemic blood circulation. SCHOSTAREZ measured how much of each compound penetrated completely though the skin into the systemic blood circulation by measuring the amounts of each compound present in lab rats' urine. SCHOSTAREZ, at Table IV, summarizes this data. Table IV shows that 5-fluoro substituted minoxidil penetrates through the skin and into the systemic blood circulation *over three times more* than plain minoxidil. *See* Table IV (urine assay shows average of only 454 μg per day of regular minoxidil, compared to 1,427 μg per day of 5-fluoro minoxidil). SCHOSTAREZ concludes, "5-fluoro minoxidil has superior absorption over the minoxidil control." Id. at col. 8, lines 19-20.

In so teaching, SCHOSTAREZ teaches away from the claimed combinations. He does this for two reasons.

First, SCHOSTAREZ teaches away from combining 5-fluoro minoxidil with skin penetrant. To the contrary, SCHOSTAREZ shows that 5-fluoro minoxidil does not need added skin penetrant. Rather, the 5-fluoro compound penetrates completely through the skin of itself, without penetration enhancer. *See* Table IV.

Second, SCHOSTAREZ teaches away from using systemic minoxidil of any kind (regular or 5-fluoro) for alopecia. This is because SCHOSTAREZ shows that both 5-fluoro and regular minoxidil precipitate severe cardiac side-effects. *See* Fig. 1, Fig. 2. While severe cardiac side-effects are appropriate for treating congestive heart failure, angina, and the like, they are unacceptable to address hair loss.

Further, SCHOSTAREZ shows that the 5-flouro compound inherently penetrates through the skin and into the systemic circulation - precipitating cardiac side effects. Neither SCHOSTAREZ nor GIBSON propose any solution to prevent this. Because the combination fails to enable the claim, the combination cannot render the claims obvious.

ZUPAN Does Not Anticipate
Claims 1, 2, 12, 13

Claims 1, 2, 12, and 13 stand rejected as anticipated under 35 U.S.C. § 102(b) by ZUPAN *et al.* Applicant respectfully traverses, because ZUPAN actively teaches away from the claimed combinations.

ZUPAN Distinguishes Itself
From The Claimed Invention

ZUPAN teaches an improved skin penetration enhancer.

ZUPAN teaches that it is well known that a number of therapeutically active agents "enter the general circulation and produce the appropriate systemic therapeutic effect" when the agent is administered "by a number of various routes such as intravenous infusion, intramuscular injection, oral, rectal or buccal routes." Id. at col. 2, lines 6-15. ZUPAN confirms that these methods have certain disadvantages; intravenous or intramuscular injection is painful, oral administration may entail poor drug absorption in the gastrointestinal tract or degradation by stomach acid or degradation by liver enzymes. Id. at

col. 2, lines 6-38. ZUPAN thus concludes that transdermal drug delivery is superior. Id. at col. 2, lines 38 *et seq*.

ZUPAN then discusses various prior art transdermal drug delivery vehicles (*e.g.*, dimethyl sulfoxide, dimethylformamide, methyldecylsulfoxide) and their ability to make a drug penetrate "through the skin and into the general circulation." Id. at col. 2, lines 38-49. ZUPAN notes, for example, that dimethyl sulfoxide "enhances the penetration of said agents through the skin and into the general circulation, thereby overcoming most of the aforementioned problems encountered by other routes of administration." Id. at col. 2, lines 55-61. ZUPAN notes, however, that dimethyl sulfoxide has certain shortcomings (*e.g.*, teratogenicity). ZUPAN thus concludes, "It is a major object of the present invention to provide a novel agent which will enhance the dermal absorption of dermatological (i.e., therapeutic or cosmetic) agents and which will enhance the delivery through the skin and into the general circulation of systemically active therapeutic agents." Id. at col. 3, lines 12-18.

Thus, ZUPAN teaches a novel agent to "enhance the delivery through the skin and into the general circulation of systemically active therapeutic agents." ZUPAN concludes that his improved skin penetration enhancer helps both dermatological and therapeutic agents alike to absorb into the general circulation. Id. at col. 3, lines 55-63 ("The amount of dermatological agents and absorbed into the underlying tissues of the skin and the amount of systemically effective therapeutic agents absorbed into the general circulation can be dramatically increased utilizing the compositions and methods of the instant invention.").

ZUPAN Teaches Away From
The Claimed Combination

ZUPAN teaches away form the claimed combination. ZUPAN specifically mentions using his eucalyptol skin penetrant with "Sex hormones, i.e., the estrogens, androgens and progestins, especially the natural sex hormones estradiol, testosterone and progesterone." Id. at col. 8, lines 17-23. ZUPAN, however, boasts, "These agents show very poor bioavailability by the oral route, but can be well absorbed through the skin when formulated with eucalyptol." Id.; *see also* col. 6, lines 35-43 ("Eucalyptol can enhance the penetration of the hormones and increase their retention."). ZUPAN thus boasts that his penetration

enhancer is even more effective than oral administration, to deliver hormones to the systemic circulation.

ZUPAN provides ample Examples supporting this assertion. The Examples measure the amount of drug which penetrates completely through rat skin samples. Example I measures penetration through skin of procaine (a systemic anti-arrhythmic and cough-suppressant drug). Table I shows that the skin penetrant eucalyptol/ethanol allows four times more procaine to penetrate completely through the skin than does N,N-diethyl-m-toluamide/ethanol. Table II shows that pure eucalyptol allows three times more procaine to penetrate completely through the skin than does pure N,N-diethyl-m-toluamide. ZUPAN achieved similar penetration rates with other drugs including the antihypertensive drug β-blocker bupranolol, *see* TABLE III, IV and XII, and the antipyretic indomethacin, *see* TABLE V and VI. Each of these tests measure drug penetration *completely through* the skin, rather than into the skin to the hair bulbs. ZUPAN summarizes, "In every case, those formulations which contained eucalyptol delivered more of the active agent through the skin than did the corresponding commercial preparation." Id. at col. 8, lines 50-54.

ZUPAN teaches drug delivery *completely through the skin* and into the systemic circulation. ZUPAN thus fails to teach the claim limitation "penetrating the skin surface to a depth of approximately the depth of hair bulbs."

ZUPAN Fails To Enable
The Claimed Combination

ZUPAN fails to enable the claimed combination. ZUPAN teaches that his penetration enhancer can be combined with literally hundreds of possible pharmaceutically active ingredients, including β-blockers (id. at col. 7, lines 5-23); antimicrobial agents (id. at col. 7, lines 14-34 and col. 5, lines 13-34); antihypertensives (id. at col. 8, lines 11-18) and muscle relaxants (id. at col. 8, lines 24-27). As with GIBSON, *supra*, discerning which one of these millions of possible combinations would make the claimed invention, would take years of research. *See* Knowles, W.R., RULE 132 DECLARATION at ¶¶ 8-9 (5 Feb. 2001). As with GIBSON, for this reason ZUPAN fails to enable - and thus fails to anticipate - the claimed invention.

SUMMARY

The Board should:

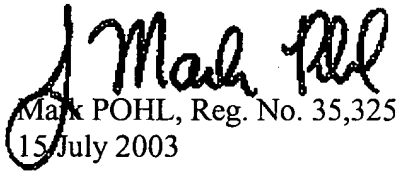
A. Reverse the objection to allegedly "new matter"; reverse the Section 112 rejection and, if desirable, ask Applicant to "make appropriate amendment to the specification ... so as to have clear support or antecedent basis in the specification for [each] term appearing in the claims" pursuant to M.P.E.P. § 608.01(o);

B. Reverse the rejections over prior art; and

C. Order the Examiner to promptly issue a NOTICE OF ALLOWANCE.

Please find enclosed (i) a NOTICE OF APPEAL; (ii) copies of the references discussed; (iii) two additional copies of this APPEAL BRIEF; (iv) a TRANSMITTAL FORM with a PETITION FOR AN EXTENSION OF TIME to respond; and (v) a FEE TRANSMITTAL FORM with the required fees.

Respectfully submitted,



Mark POHL, Reg. No. 35,325
15 July 2003

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CLAIMS ON APPEAL

1. A composition of matter intended for topical use in preventing or treating alopecia, or maintaining healthy hair, said composition of matter comprising:

a) an active compound selected from the group consisting of: a pharmaceutically or cosmetically effective topical amount of a 5α-reductase inhibitor and minoxidil, and

b) a non-retinoid penetration enhancer, said penetration enhancer present in a concentration sufficient to aid said active compound in penetrating the skin surface to a depth of approximately the depth of hair bulbs.

2. The composition of claim 1, wherein said active compound comprises a 5α-reductase inhibitor.

3. The composition of claim 1, wherein said active compound comprises minoxidil.

4. The composition of claim 3, further comprising a 5α-reductase inhibitor.

5. The composition of claim 4, wherein the ratio of penetration enhancer to 5α-reductase inhibitor to minoxidil in the composition is approximately 0.5 grams : 1 gram.

7. The composition of claim 5, wherein said 5α-reductase inhibitor is present in a concentration of 0.5 grams per 4 ounces of finished liquid.

8. An article of manufacture comprising the composition of claim 4, labeled for topical cosmetic use in maintaining normal, healthy hair.

9. An article of manufacture comprising the composition of claim 4, labeled for topical pharmaceutical use in preventing or treating a disease.

10. The composition of claim 9, wherein said disease comprises alopecia.

11. The composition of claim 4, further comprising a sunscreen in an amount effective to screen radiation.

12. A method for preventing or treating alopecia, or maintaining healthy hair, said method comprising:

a) Topically administering an active compound selected from the group consisting of: a pharmaceutically or cosmetically effective topical amount of a 5α-reductase inhibitor and minoxidil, together with

b) a non-retinoid penetration enhancer, said penetration enhancer present in a concentration sufficient to aid said active compound in penetrating the skin surface to a depth of approximately the depth of hair bulbs.

13. The method of claim 12, wherein said active compound comprises a 5α-reductase inhibitor.

14. The method of claim 12, wherein said active compound comprises minoxidil.

15. The method of claim 14, wherein said active compound further comprises a testosterone blocker.

16. The method of claim 15, wherein the ratio of penetration enhancer to 5α-reductase inhibitor to minoxidil in the composition is approximately 0.5 grams : 1 gram.

18. The method of claim 16, wherein said 5α-reductase inhibitor is present in a concentration of 0.5 grams per 4 ounces of finished liquid.

19. The method of claim 15, labeled for topical cosmetic use in maintaining normal, healthy hair.

20. The method of claim 15, labeled for topical pharmaceutical use in preventing or treating a disease.

21. The method of claim 20, wherein said disease comprises alopecia.

22. The method of claim 15, further comprising a sunscreen in an amount effective to screen radiation.

REFERENCES CITED

Legal Authority

THE MERCK INDEX, ¶ 7947 (13th ed. 2001)
In re Barr, 444 F.2d. 588 (C.C.P.A. 1971).
Biogen, Inc. v. Amgen, Inc., 973 F.Supp. 39 (D.Mass. 1997)
Elan Pharma., Inc. v. Mayo Fdn. For Med. Educ., 304 F.3d 1221 (Fed.Cir. 2002)
In re Hoeksema, 399 F.2d 269 (Fed. Cir. 1968)
Purdue Pharma L.P. v. Faulding Inc., *slip op.* (Fed.Cir. 25 Oct. 2000)
In re Wakefield, 422 F.2d 897, 904 (C.C.P.A. 1970)

Prior Art References

BAZZANO, United States Letters Patent No. 5,183,817
GIBSON, United States Letters Patent No. 5,015,470,
GROLLIER, United States Letters Patent No. 5,192,534
SCHOSTAREZ, United States Letters Patent No. 5,373,012
ZUPAN, United States Letters Patent No. 4,440,777

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ution: Gas may act as a simple asphyxiant and mild an-tic. Direct contact with liquid may cause skin burns. *See y's Industrial Hygiene and Toxicology* **Vol. 2B,** G. D. Clay-F. E. Clayton, Eds. (John Wiley & Sons, Inc., New York, 1994) p 1244-1245.

E: In polymerized form as polypropylene for plastics and et fibers. Chemical intermediate in the manuf of acetone, opylbenzene, isopropanol, isopropyl halides, propylene ox-acrylonitrile, cumene.

942. Propylene Chlorohydrin. [78-89-7] 2-Chloro-1-anol; 2-chloropropyl alcohol. C_3H_7ClO; mol wt 94.54. C 1%, H 7.46%, Cl 37.50%, O 16.92%. $CH_3CHClCH_2OH$. rless liquid; pleasant odor. d^{20} 1.103; bp 133-134°; n_D^{20} 02. Sol in water, alcohol, etc. LD_{50} orally in rats: 0.22 g; by skin penetration in rabbits: 0.48 ml/kg, Smyth *et al., Ind. Hyg. Assoc. J.* **30,** 470 (1969).

E: In prepn of propylene oxide *(q.v.).*

943. *sec*-Propylene Chlorohydrin. [127-00-4] 1-Chlo-propanol; 1-chloroisopropyl alcohol. C_3H_7ClO; mol wt 4. C 38.11%, H 7.46%, Cl 37.50%, O 16.92%. $ClCH_2$-OH)CH_3.
rless liquid. d^{20} 1.115; bp 126-127°; n_D^{20} 1.4392. Sol in r, alcohol, etc.

944. Propylenediamine. [78-90-0] 1,2-Propanediamine. $_6N_2$; mol wt 74.12. C 48.61%, H 13.60%, N 37.79%. CH_3-$NH_2)CH_2NH_2$. Prepd from propylene dibromide and al-olic ammonia at 100°.
tremely hygroscopic, strongly alkaline liq. Rapidly ab-s moisture to form a hemihydrate. d^{15} 0.878 in anhydr form. -120°. Very sol in water. *Keep tightly closed.*
E: In conjunction with cupric sulfate it is a very sensitive ent for mercury.

945. Propylene Dibromide. [78-75-1] 1,2-Dibromopro-: $C_3H_6Br_2$; mol wt 201.89. C 17.85%, H 3.00%, Br 6%. $CH_3CHBrCH_2Br$. Prepd from propyl bromide and Br e presence of $AlCl_3$ or $AlBr_3$.
olorless liquid. mp −55°; bp 140-142°; n_D^{20} 1.5203; d^{20} Slightly sol in water; miscible with organic solvents.

946. Propylene Dichloride. [78-87-5] 1,2-Dichloropro-: $C_3H_6Cl_2$; mol wt 112.99. C 31.89%, H 5.35%, Cl 5%. $CH_3CHClCH_2Cl$. Prepd from propyl chloride and Sb_2-. Toxicity data: H. F. Smyth *et al., Am. Ind. Hyg. Assoc. J.* 470 (1969).
lammable, mobile liq. Odor of chloroform. d_{25}^{25} 1.159; bp 06°. Solidifies below −70°. n_D^{20} 1.4388. Flash point (ASTM cup) 21°C (70°F). Despite the low flash pt it does not catch adily in industrial applications. Fire pt 38°. Slightly sol vater; miscible with organic solvents. LD_{50} orally in rats:) ml/kg (Smyth).
aution: Potential symptoms of overexposure are eye, skin respiratory system irritation; drowsiness, lightheadedness; r and kidney damage. Potential occupational carcinogen. *NIOSH Pocket Guide to Chemical Hazards* (DHHS/NIOSH 140, 1997) p 268.
SE: Oil and fat solvent; in dry cleaning fluids; in degreas-n insecticidal fumigant mixtures.

947. Propylene Glycol. [57-55-6] 1,2-Propanediol; me-l glycol; 1,2-dihydroxypropane. $C_3H_8O_2$; mol wt 76.09. C 35%, H 10.60%, O 42.05%. $CH_3CHOHCH_2OH$. Prepn m glycerol: Raschig, Prahl, *Ber.* **61,** 185 (1928). Prepn of otatory propylene glycol from hydroxyacetone by yeast re-ction: Levene, Walti, *Org. Syn.* **coll. vol. II,** 545 (1943). thesis of S-(+)-form: C. Melchiorre, *Chem. Ind. (London)* 218. Manuf from propylene oxide by hydration: *Faith, ys & Clark's Industrial Chemicals,* F. A. Lowenheim, M. Moran, Eds. (Wiley-Interscience, New York, 4th ed., 1975) 688-691. Toxicity data: W. Bartsch *et al., Arzneimittel-rsch.* **26,** 1581 (1976). GC/MS determn in plasma: C. Gia-tti *et al., Biomed. Environ. Mass Spectrom.* **18,** 592 (1989). view of toxicity, metabolism and biochemistry: Ruddick, xicol. Appl. Pharmacol. **21,** 102 (1972); of toxicology and human exposure: *Toxicological Profile for Ethylene Glycol and Propylene Glycol* (US DHHS, PB98-101109, 1997) 250 pp.

***dl*-Form.** Hygroscopic, viscous liquid. Slightly acrid taste. d_4^{25} 1.036. mp −59°. bp_{760} 188.2°; bp_{400} 168.1°; bp_{200} 149.7°; bp_{100} 132.0°; bp_{60} 119.9°; bp_{40} 111.2°; bp_{20} 96.4°; bp_{10} 83.2°; bp_5 70.8°; $bp_{1.0}$ 45.5°. Flash pt, open cup: 210°F (99°C). Miscible with water, acetone, chloroform. Sol in ether. Will dissolve many essential oils, but is immiscible with fixed oils. It is a good solvent for rosin. Under ordinary conditions propylene glycol is stable, but at high temps it tends to oxidize giving rise to products such as propionaldehyde, lactic acid, pyruvic acid and acetic acid. LD_{50} orally in rats: 25 ml/kg (Bartsch).

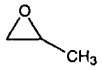
***l*-Form.** bp_{12} 88-90°, bp_{760} 187-189°. $[\alpha]_D^{20}$ −15.0°.

***d*-Form.** bp_{14} 94-96°. $[\alpha]_D^{20}$ +15.84%° (neat). d^{25} 1.04.

USE: Nontoxic antifreeze in breweries and dairy establishments. Substitute for ethylene glycol and glycerol. In the manuf of synthetic resins and de-icing solutions. Emulsifier in foods; solvent for food colors and flavors. Pharmaceutic aid (humectant, solvent). As mist to disinfect air; to create artificial smoke and mist for theatrical use.

:THERAP CAT (VET): Glucogenic (orally) in ruminants.

7948. Propylene Oxide. [75-56-9] Methyloxirane; propene oxide. C_3H_6O; mol wt 58.08. C 62.04%, H 10.41%, O 27.55%. Results from the action of KOH (aq) on propylene chlorohydrin. Toxicity: H. F. Smyth *et al., J. Ind. Hyg. Toxicol.* **23,** 259 (1941). Toxicological comparison with ethylene oxide, *q.v.*: E. Agurell *et al., Mutat. Res.* **250,** 229 (1991). *Reviews:* Holden in *Glycols,* G. O. Curme, F. Johnston, Eds., A.C.S. Monograph Series no. **114** (Reinhold, New York, 1952) pp 250-261; *Faith, Keyes & Clark's Industrial Chemicals,* F. A. Lowenheim, M. K. Moran, Eds. (Wiley-Interscience, New York, 4th ed., 1975) pp 692-697; R. O. Kirk, T. J. Dempsey in *Kirk-Othmer Encyclopedia of Chemical Technology* **vol. 19** (Wiley-Interscience, New York, 3rd ed., 1982) pp 246-274. Review of manufacturing processes: *Chem. & Eng. News* **70,** 9-12 (Mar. 2, 1992); of carcinogenic risk: *IARC Monographs* **60,** 181-213 (1994).



Colorless ethereal liquid. *Extremely flammable.* d_4^0 0.859. mp −112.13°. bp 34.23°. Flash pt, closed cup: −31°F (−35°C). Soly in water (20°): 40.5% by wt; soly of water in propylene oxide: 12.8% by wt; miscible with alcohol, ether. LD_{50} orally in rats: 1.14 g/kg (Smyth).

Caution: Potential symptoms of overexposure are irritation of eyes, skin and respiratory system; blistering and burns. *See NIOSH Pocket Guide to Chemical Hazards* (DHHS/NIOSH 97-140, 1997) p 270. This substance is reasonably anticipated to be a human carcinogen: *Ninth Report on Carcinogens* (PB2000-107509, 2000) p III-193.

USE: Chemical intermediate in prepn of polyethers to form polyurethanes; in prepn of urethane polyols and propylene and dipropylene glycols; in prepn of lubricants, surfactants, oil demulsifiers. As solvent; fumigant; soil sterilant.

7949. Propyl Ether. [111-43-3] 1,1′-Oxybispropane; dipropyl ether. $C_6H_{14}O$; mol wt 102.17. C 70.53%, H 13.81%, O 15.66%. $C_3H_7OC_3H_7$. Obtained by heating propyl alcohol with benzenesulfonic acid.

Mobile liquid. Extremely flammable. d_4^{20} 0.7360; mp −122°; bp 89-91°; n_D^{20} 1.3807. Flash pt, open cup: −5°F (−20°C). Slightly sol in water; sol in alcohol, ether. Highly volatile. Tends to form explosive peroxides, esp when anhydr. Do not allow to evaporate to near dryness.

7950. Propyl Formate. [110-74-7] Formic acid propyl ester. $C_4H_8O_2$; mol wt 88.10. C 54.53%, H 9.15%, O 36.32%. $HCOOC_3H_7$.

Colorless liquid; pleasant odor. d^{20} 0.901; mp −93°; bp 81-82°. Flash pt, closed cup: 27°F (−3°C). n_D^{20} 1.3771. Sol in 45 parts water; misc with alcohol, ether. LD_{50} orally in rats: 3980 mg/kg, P. M. Jenner *et al., Food Cosmet. Toxicol.* **2,** 327 (1964).

C

United States Court of Customs and Patent Appeals.

Application of Charles R. BARR et al.

Patent Appeal No. 8429.

July 8, 1971, Rehearing Denied Oct. 7, 1971.

Proceeding in the matter of an application for a patent. The patent office board of appeals, Serial No. 507,975, affirmed the examiner's rejection of certain of the involved claims as failing to define the invention properly, and the applicant appealed. The United States Court of Customs and Patent Appeals, Rich, J., held that claims 23, 24, 26-30, 32-35 of application for patent relating to photographic elements and processes utilizing mercaptan-forming couplers were improperly rejected as being indefinite, negative and unsupported by specification. The Court further held that claim 25 of the application was properly rejected for failure to point out and distinctly claim the subject matter regarded as the invention.

Affirmed in part and reversed in part.

Almond, J., dissented and filed opinion in which Baldwin, J., joined.

West Headnotes

[1] Patents ⇨101(4)
291k101(4) Most Cited Cases

[1] Patents ⇨101(6)
291k101(6) Most Cited Cases

Claims 23, 24, 26-30, 32-35 of application for patent relating to photographic elements and processes utilizing mercaptan-forming couplers were improperly rejected as being indefinite, negative and unsupported by specification. 35 U.S.C.A. §§ 101, 103, 112.

[2] Patents ⇨101(9)
291k101(9) Most Cited Cases

Although court of customs and patent appeals, in contrast to court adjudicating infringment suit on issued patent, will give claims yet unpatented broadest reasonable interpretation consistent with specification, disclosure may serve as dictionary for terms appearing in claims and in such instances disclosure may be used in interpreting the claims and in determining their scope.

[3] Patents ⇨101(5)
291k101(5) Most Cited Cases

Applicant for patent on chemical compound may invoke portion of statute providing that element in claim for combination may be expressed as means or step for performing specific function without recital of structure, material, or acts in support thereof to justify specification of one or more elements of claimed compound "functional" terms, and those "function" terms may be "negative". 35 U.S.C.A. § 112.

[4] Patents ⇨101(5)
291k101(5) Most Cited Cases

Claim 25 of application for patent relating to photographic elements and processes utilizing mercaptan-forming couplers was properly rejected for failure to point out and distinctly claim the subject matter regarded as the invention. 35 U.S.C.A. § 112.

Patents ⇨328(2)
291k328(2) Most Cited Cases

3,227,551, 3,227,554. Cited.

****588 *1390** James R. Frederick, Ogden H. Webster, Rochester, N.Y., attorneys of record, for appellants.

S. Wm. Cochran, Washington, D.C., for Commissioner of Patents; Raymond E. Martin, Washington, D.C., of counsel.

Before RICH, ALMOND, BALDWIN and LANE, Judges, and DURFEE, Judge, United States Court of Claims, sitting by designation.

RICH, Judge.

This appeal is from the decision of the Patent Office Board of Appeals affirming the examiner's rejection of claims 23-30 and 32-35 in appellants' application entitled 'Photographic Elements and Processes Utilizing Mercaptan-Forming Couplers,' serial No. 507, 975, filed ***1391** June 14, 1965, a division of application serial No. 270, 709, filed April 4, 1963, which matured into patent No. 3,227,554 on January 4, 1966. The appealed claims, all of which are for photographic color couplers, were 'rejected as failing to define the invention properly, under 35 U.S.C. 112 * * *.' Claim 36, for a single chemical compound, stands allowed. We affirm in part and reverse in part.

****589** THE INVENTION

A 'coupler' in this context is 'a compound in a color-photography emulsion or developer solution that combines with the oxidized developer to form a dye.' Webster's Third New International Dictionary (1966). The particular couplers here involved are of the general formula COUP-S-R wherein COUP is a coupler radical, S is a monothio radical (i.e., a sulfur atom) substituted in the

coupling position of the COUP radical, and R is an organic radical. The essence of the invention is the use of the monothio radical to link known coupler radicals to certain other known organic radicals, resulting in the formation of diffusible mercaptans of the formula R-SH and photographic dyes when the coupler is reacted with a suitable developing agent. These mercaptans inhibit the growth of dye particles, increasing the sharpness of the resulting photograph. Allowed claim 36 recites a single chemical compound; the twelve claims on appeal recite classes of compounds, and it is the manner in which they do so which has led to this appeal.

We set forth claim 23, the broadest on appeal, as illustrative:

23. A photographic color coupler capable of forming a dye and a mercaptan when reacted with oxidized aromatic primary amino color developing agent and having the formula COUP-S-R wherein

COUP is a photographic color coupler radical selected from the group consisting of a 5-pyrazolone coupler radical and an open-chain ketomethylene coupler radical,

COUP having substituted in its coupling position the monothio radical; and

R is an organic radical incapable of forming a dye with said oxidized developing agent and being selected from the group consisting of an alkyl radical, a cycloalkane radical, an aryl radical and a heterocyclic radical containing at least one hetero atom selected from the group consisting of oxygen, sulphur and nitrogen.

THE REJECTION

No prior art is relied on.

The gist of the principal rejection, as expressed by the examiner, is that the claims 'appear to read on vast numbers of compounds, whose only common feature is a thioether linkage.' This fact, he wrote, renders the claims 'so broad as to be virtually meaningless,' thereby ***1392** failing 'to point out what applicants regard as their invention with the specificity required by 35 U.S.C. 112.' Specifically, he said the terms 'a 5-pyrazolone coupler radical' and 'an open-chain ketomethylene coupler radical' (one or the other or both of which are used in every claim on appeal) render the claims 'indefinite' because they read on 'any substituted derivative' whereas 'Only a relatively small, unrepresentative number of particular radicals falling within such terminology is supported by the specification.' Similarly, the examiner stated that the terms 'aryl,' 'alkyl,' and 'herterocyclic' did not 'meet the requirements of 35 U.S.C. 112,' apparently on the ground that the use of such broad terms was not supported by the specification since he cited In re Sus, 306 F.2d 494, 49 CCPA 1301 (1962).

Additionally, the examiner held that the phrase 'incapable of forming a dye with said oxidized developing agent' is 'unduly functional at a point of novelty,' that the terms 'coupling position,' '5-pyrazolone coupler radical,' and 'openchain ketomethylene' were impermissibly 'indefinite,' and that 'Appellants' use of 'a phenyl' in claims 24, 25 and 30 involves a distortion of the term' because the specific radical recited in claim 25, which depends from claim 24, [FN1] is not in fact a phenyl radical as that term is commonly understood.

> FN1. Claim 30 is equivalent to claim 24 in this respect.

The Board of Appeals affirmed all the examiner's rejections. Concerning ****590** whether use in the claims of the broad terms '5-pyrazolone coupler radical' and 'open-chain ketomethylene coupler radical' was supported by the specification, the board noted that appellants had disclosed thirty-seven specific examples of the former and forty specific examples of the latter but concluded that the specific examples given were not 'sufficiently representative' of the 'so-called classes * *. * delineated by the claims * * *.' The recitation of the R group it found similarly impermissible because it is 'even broader' than the terminology used to delimit the photographic color coupler radicals.

Concerning the secondary rejections, the board held that 'claims 23, 24, 26, 30, 31 and 32 do not identify the coupling position and this alone would render these claims indefinite and too broad,' and the phrase 'incapable of forming a dye with said oxidized developing agent' it found objectionable both for being 'functional' and for being 'negative.' While it did not comment specifically on the examiner's other grounds of rejection, it did state that it found 'no reversible error' in the examiner's rejection of all claims on the ground that the limitations placed by the claims on the COUP and R moieties were 'so broad and indefinite that no definite or determinable group of compounds is set ***1393** forth' and of claim 25 on the ground that it 'amounts to a distortion of the term 'phenyl radical' * * *.'

OPINION

This opinion is in five sections, the first three dealing with the general rejections for indefiniteness under the second paragraph of 35 U.S.C. 112, the fourth dealing with the rejections under the first paragraph of 35 U.S.C. 112, and the last dealing with the specific rejection of claim 25 under the second paragraph of 35 U.S.C. 112.

I. Are the terms '5-pyrazolone coupler radical' and

'open-chain ketomethylene coupler radical' indefinite?

[1] To rephrase the question in terms of the statute, does the use in the claims of the terms '5-pyrazolone coupler radical' and 'open-chain ketomethylene coupler radical' cause the claims to fail in particularly pointing our and distinctly claiming the subject matter which appellants regard as their invention? To answer this question, the claims must be construed from the standpoint of a person skilled in the relevant art. In this regard we note (1) that each of the appealed claims is expressly directed to 'photographic color couplers,' (2) that the first paragraph of the specification states that 'This invention relates to photography, and more particularly, to photographic elements and processes utilizing a new class of photographic color couplers,' (3) that each object of the invention recited in the specification concerns the photographic art, and (4) that the only utility of the invention asserted in the specification and shown in the examples is in the photographic art. From all this we conclude that the specification, including the claims with which it concludes, is directed to those skilled in the photographic art and must be construed from the standpoint of a person skilled therein.

Appellants rely heavily on the fact that United States patents, including the patent which matured from the parent of this application, have issued containing the terminology now controverted. This they cite as evidence that 'Patent Office Examiners skilled in photographic chemistry recognize that '5- pyrazolone' and 'open-chain ketomethylene' constitute a distinct, identifiable group of color coupler radicals.' [FN2] While we agree with ****591** the solicitor that these patents are ***1394** not weighty evidence of art recognition of the controverted terms 'in the absence of proof, or even an allegation, that the patented files show that the 'art-recognized group' issue was raised therein, and resolved in appellants' favor,' [FN3] we note that neither the examiner nor the board gave any reason (for instance, the simple statement that they had never seen the terms used before and would like to see examples of their use in literature in the art) for their distrust of appellants' terminology.

> FN2. The present application was apparently assigned to a section of the Patent Office other than that to which the applications from which the patents relied upon were assigned, and both a letter of appellants to the examiner and appellants' brief before the Board of Appeals contain plaintiff requests that the reader 'consult any one of the expert photographic Examiners in the photographic examining group' if he doubted appellants' assertion that 5-pyrazolone coupler radicals and open-chain ketomethylene coupler radicals 'are notoriously well known in the art.'
>
> FN3. Moreover, both such patents which were properly in the record before the Patent Office and which are in the record before us were issued to appellants here and assigned to the real party in interest here, which suggests that the terms may be 'art-recognized' only in appellants' own laboratory.

Thus we are faced with appellants' fervent protestation that 'Open-chain ketomethylene and 5-pyrazolone photographic color coupler radicals constitute distinct, identifiable groups of radicals recognized by those skilled in the photographic art,' as evidence of which they have cited the use of those terms in the claims of two presumptively valid U.S. patents, [FN4] on the one hand, and the solicitor's equally fervent, but unsupported, protestation that 'The (appellants') contention regarding art recognized classes lacks merit' on the other. The solicitor has not directed our attention to any evidence in the record or any indication in generally accepted references in the art that a competent photographic chemist could not ascertain whether any given chemical did or did not contain either a 5-pyrazolone coupler radical or an openchain ketomethylene coupler radical and therefore whether the appealed claims did or did not read on the given chemical to that extent, and what we find in what we take to be generally accepted references is to the contrary. We note, for instance, that in Vittum and Weissberger, The Chemistry of Dye-Forming Development, 2 Journal of Photographic Science 81 (1954), cited by appellants, the authors divide 'nearly all' of the 'diverse compounds' known to be useful as couplers into three groups: (a) openchain methylene compounds, (b) cyclic methylene compounds, and (c) methine compounds. While Vittum and Weissberger do not specifically mention openchain ketomethylene couplers, we think it indisputable that, if photographic chemists would recognize open-chain methylene couplers in general, they would recognize open-chain ketomethylene couplers in particular. Similarly, while Vittum and Weissberger state only that 'The most valuable couplers of this group (i.e., the cyclic methylene compounds) are the pyrazolones which are widely used as magenta couplers,' we note that Kirk-Othmer, Encyclopedia of Chemical Technology (2d ed. 1968), Vol. 16 at 772, defines the 5-pyrazolone structure, and Vol. 5 at 824, in the article entitled 'Color Photography,' states that 'The ***1395** most important class of couplers for magenta dye formation are the derivatives of 5-pyrazolones,' indicating that 5-pyrazolone color couplers are well known to the photographic art. [FN5]

> FN4. U.S. Patent No. 3,227,551, and U.S. Patent No. 3,227,554, both issued Jan. 4, 1966, and assigned to Eastman Kodak Company.
>
> FN5. We do not use the above references as a basis for the taking of judicial notice that the controverted phrases are artrecognized (which

> would eliminate the need for our reliance on the two patents of record) because we are not sure that this fact is indisputable among reasonable men. McCormick on Evidence, 324, p. 689 (1954). However, we are of the view that these extra-record references may be used to bolster a weak point which is supported by some evidence in the record even though we would decline to use them by themselves as a basis for the taking of judicial notice if there were no evidence at all in the record in support of the point. Cf. In re Boon, 439 F.2d 724, 727-728, 58 CCPA (1971).

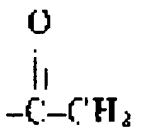
In his brief on appeal, the solicitor argued the weakness of the appellants' proof and emphasized the breadth of appellants' ****592** claims. [FN6] While we have already noted that appellants' case might well have been much stronger (if, for instance, the affidavit which appears in the printed transcript but which is not a part of the official record because of the lateness of its submission had been subimtted earlier), under the circumstances appellants have persuaded us that their claims are just as definite as a claim for 'all compounds containing sulfur,' a claim which might not be in compliance with the first paragraph of 35 U.S.C. 112, depending upon the disclosure contained in the specification, and which would certainly be too broad in the sense of 35 U.S.C. 103, but which would be fully in compliance with the second paragraph of section 112, assuming the applicant regarded his invention to consist of 'all compounds containing sulfur.' Accordingly, we cannot affirm the board's rejection on this ground.

> FN6. This latter argument we regard as beside the point, for there is no indication in the record that the appellants regard their invention as encompassing anything less than the broad field claimed.

II. Does the use of the term 'coupling position' in the claims make them indefinite?

Independent claims 23, 24, 26, 30, and 32 recite the COUP radical then recite the substitution of the monothio radical S in 'its coupling position,' and the other claims on appeal incorporate the 'coupling position' recitation by operation of law. 35 U.S.C. 112, second paragraph, second sentence. According to the specification, it is 'well known to those skilled in the photographic art' what 'the coupling position' of COUP radicals of the type recited is. Specifically,

The 5-pyrazolone coupler radicals couple at the carbon atom in the 4- position, * * * and the open-chain ketomethylene coupler radicals couple at the carbon atom forming the methylene moiety (e.g.,



denoting the coupling position).

***1396** The examiner in his Answer, however, seems to have questioned the accuracy of the above assertion, stating that

* * * most '5-pyrazolone' radicals and 'open-chain ketomethylene' radicals have more than one 'coupling position,' and these are not necessarily in the positions designated * * *

and citing 4-4-dimethyl-3-(2-hydroxy-phenyl)-5-pyrazolone as a compound which 'might be 'a 5-pyrazolone coupler radical' with the coupling position being the 5-position in the phenyl ring.' In affirming, the board stated that the failure of the claims to 'identify the coupling position' was by itself sufficient to render them 'indefinite and too broad.' The claims would clearly be definite if, despite the lack of specific recitation of the coupling position in the claim, the recitation of 'the coupling position' of a 5- pyrazolone coupler radical and of an open-chain ketomethylene coupler radical would be understood by those skilled in the photographic art to refer to the single, definite positions set forth in appellants' specification. This being so, we take it that the board must have (1) accepted the examiner's contention that there are a plurality of 'coupling positions' on the recited COUP radicals, (2) read the claims as referring to a single, unspecified one of those 'coupling positions,' and (3) found that appellants had failed to 'particularly point out' in their claims at which of the plurality of possible coupling positions the monothio radical was substituted in the particular photographic color couplers, thereby failing to point out what they regard as their invention.

[2] While we are mindful of our declaration in In re Prater, 415 F.2d 1393, 56 CCPA 1381 (1969), that this court, in contrast to a court adjudicating an infringement suit on an issued patent, will give 'claims yet unpatented * * *the ****593** broadest reasonable interpretation consistent with the specification,' id., 415 F.2d at 1404, 56 CCPA at 1396, it is also settled patent law that the disclosure may serve as a dictionary for terms appearing in the claims and that in such instances the disclosure may be used, even by this court, in interpreting the claims and in determining their scope. In re Vogel, 422 F.2d 438, 441, 57 CCPA 920, 924 (1970). In our view, this is such a case, for the specificity with which appellants have set forth what they mean by the controverted phrases is the practical equivalent of a section in their specification headed 'Lexicography.' Even if it is true that 'most '5-pyrazolone' radicals and 'open-chain ketomethylene' radicals have more than one 'coupling position" in the general sense of that phrase, the portion of

the specification quoted at the beginning of this section defines with great particularity precisely what appellants meant by the phrase. So interpreted, ***1397** their claims do particularly point out and distinctly claim, so far as this issue is concerned, the subject matter which the appellants regard as their invention and therefore comply with the second paragraph of section 112.

(1) III. Does the use of the phrase 'incapable of forming of dye with said oxidized developing agent' in the claims make them indefinite?

The board affirmed the examiner's rejection of all claims on the ground that the limitation 'incapable of forming a dye with said oxidized developing agent' placed on the organic radical R is 'negative and functional.' On appeal, appellants argue that, since the claimed compounds are composed of known classes of radicals, these radicals can be specified in terms of their function without recitation of structure within the meaning of the third paragraph of 35 U.S.C. 112. [FN7] The solicitor, on other hand, has argued that

> FN7. 35 U.S.C. 112, third paragraph, reads:
> An element in a claim for a combination may be expressed as a means or step for performing a specified function without the recital of structure, material, or acts in support thereof, and such claim shall be construed to cover the corresponding structure, material, or acts described in the specification and equivalents thereof.

* * * paragraph 3 (of 35 U.S.C. 112) is applicable to a plural step process, a mechanical combination of elements, a plurality of compounds taken in combination (a composition), but not (to) a compound.

The gist of the solicitor's argument, as we understand it, is that the third paragraph of section 112 refers only to combinations each element of which is itself patentable subject matter (i.e., which could be separately patented, subject to the conditions and requirements of Title 35) and that radicals are not patentable subject matter.

At the outset we note that it has not been argued that 'functional' language in a claim is prohibited except as authorized by the permissive third paragraph of section 112.7 Indeed, the solicitor ends the portion of his brief on this point with the caveat that his arguments are

* * * not to say that functional language could not be used in a claim to characterize any such 'element' (i.e., 'an 'element' such as a chemical compound or a single intergral mechanical component or element, such as a nail') provided the claim otherwise satisfies the requirements of Section 112, paragraph 2.

However, appellants have expressly sought, and have been denied, 'the benefit of the third paragraph of 35 U.S.C. 112,' presenting for our determination an interesting extension of the issue before us in In re Fuetterer, 319 F.2d 259, 50 CCPA 1453, (1963).

***1398** In the Fuetterer case we recided that the use of functional statements in claims to limit a class of chemical compounds (salts) used as one element of a composition of matter 'is specifically sanctioned by the third paragraph of ****59**435 U.S.C. 112.' [FN8] As the solicitor points out, the case is not directly in point because it 'dealt with a composition, not a compound.' Nevertheless, we feel that its rationale, if not its holding, is controlling here. There the solicitor argued that 'the last paragraph of 35 U.S.C. 112 is by its very language limited to claimed combinations involving mechanical structures or apparatus and methods,' but we disagreed, noting our agreement with the statement in Federico's Commentary on the New Patent Act, 35 USCA Vol. 1, p. 25 (1954), that the word 'combination' in this paragraph includes 'not only a combination of mechanical elements, but also a combination of substances in a composition claim, or steps in a process claim.' Here the solicitor has expanded his argument just enough to concede the narrow holding of Fuetterer, and once again we are not persuaded that the clear words of the statute should be given so illiberal an interpretation.

> FN8. Only two judges joined the opinion of the court in Fuetterer. Two judges dissented, and one judge concurred 'in result only,' without opinion. However, the opinion of the dissenting judges argues that Fuetterer's specification failed to teach 'which salts, other than the four disclosed, are capable of performing the desired function" it does not suggest that functional expressions are per se inadequate to particularly point out and distinctly claim classes of compounds used as elements of compositions. Furthermore, both judges who dissented in Fuetterer joined the unanimous opinion in In re Boller, 332 F.2d 382, 51 CCPA 1484 (1964), a case in which the same panel of judges hearing Fuetterer reaffirmed the propriety of using functional language to describe one element in claims for a composition of resin, neutralizing agent, and water. Id. 332 F.2d at 386, 51 CCPA at 1488.
> See also Locklin v. Switzer Bros., Inc., 299 F.2d 160, 165-166 (9th Cir. 1961) (approving a product-by-process claim in which the amount of one reactant was described as 'an amount * * * sufficient to render said condensation product substantially insoluable in aromatic hydrocarbon solvents but insufficient to render it thermosetting'), cert. denied, 369 U.S. 861, 82

S.Ct. 950, 8 L.Ed.2d 18 (1962).

Speaking broadly but giving each of the disputed words their normal meaning, all 'compositions of matter' are 'combinations' if they consist of two or more substances in some degree of corelationship. The inorganic salts in Fuetterer were substances which occupied space and had mass, so they were matter, and they coacted with rubber, vulcanizing agent, reinforcing agent, protein, and/or carbohydrate to produce a desired result (improving the wet traction of tires), so the salts were held to constitute one element of a 'combination' as that word is used in the third paragraph of section 112. Here, the controverted radicals are matter, for they too occupy space and have mass, and even more clearly than in Fuetterer they coact with the other two radicals recited to produce a desired result-- namely, 'A photographic color coupler capable of forming a dye and a mercaptan when reacted with oxidized aromatic primary amino color developing agent.'

***1399** The solicitor has argued that a combination is not patentable unless every element of the combination 'could qualify as a patentable element' (i.e., is statutory subject matter). He has cited no authority for this proposition, and we decline to adopt it. In our view, the categories of statutory subject matter are set forth in 35 U.S.C. 101; chemical compounds are clearly included as one kind of 'composition of matter'; and whether the 'elements' of chemical compounds are themselves statutory subject matter we deem irrelevant to the question on appeal.

Accordingly, we hold that a radical constituting an element of a claimed chemical compound is an 'element in a claim for a combination' within the meaning of 35 U.S.C. 112, third paragraph.

There remains for consideration the board's rejection of all claims on the ****595** ground that the recital 'incapable of forming a dye with said oxidized developing agent' is 'negative.' [FN9] However, we feel that this rejection needs little comment in view of our decision in In re Wakefield, 422 F.2d 897, 57 CCPA 959 (1970), where we rejected a similar contention. Id. 422 F.2d at 904, 57 CCPA at 967, 164 USPQ at 641. Again, the real 'complaint seems to be that a very large number of substances are encompassed by the claims,' and again we see no problem with the under the second paragraph of section 112, so long as the scope of the claim is definite. Here again the boundaries of the patent protection sought are set forth definitely, albeit negatively, and here again we hold that challenged claim complies with the second paragraph of 112 in this respect.

> FN9. This rejection was contained in the first office action, but, after appellants responded that rejection on this ground 'does not appear to be pertinent in view of the Commissioner's notice published May 10, 1965, 145 U.S.P.Q. No. 6, page II,' the examiner did not raise it again. Thus, it appears to have been a new ground of rejection when the board resurrected it in its opinion.

[3] In summary, we hold that an applicant may invoke the third paragraph of section 112 to justify the specification of one or more elements of a claimed compound in 'functional' terms, [FN10] and that those 'functional' terms may be 'negative.' The real issue in any such case is not whether the recital is 'functional' or 'negative,' but whether the recital sets definite boundaries on the patent protection sought-- that is, whether those skilled in the relevant art can determine what the claim does or does not read on. Judged by this standard, we think it clear that the controverted language complies with the second paragraph of section 112.

> FN10. At least where, as here, the functional language modifies known classes of radicals.

IV. Is the claim terminology supported by the specification?

All claims have been rejected on the ground that the terms '5- ***1400** pyrazolone coupler radical' and 'open-chain ketomethylene coupler radical' and the various phrases used in specifying the R radical [FN11] are insufficiently supported in the specification-- or, in the words of the statute, on the ground that the specification does not contain a written description of the manner of making and using the invention in such terms as to enable any person skilled in the photographic art to make and use the same. However, since it is not questioned that the specification teaches how to make and use at least certain embodiments of the invention, the question is really whether the applicants have enabled as broadly as they have claimed.

> FN11. Claim 23: 'selected from the group consisting of an alkyl radical, a cycloalkane radical, an aryl radical and a heterocyclic radical containing at least one hetero atom selected from the group consisting of oxygen, sulfur and nitrogen.'
> Claims 24 and 30: 'a phenyl radical.'
> Claim 25: 'a 3-octadecycarbamylphenyl radical.'
> Claims 26 and 32: 'a heterocyclic radical having 1 to 4 hetero-nitrogen atoms.'
> Claims 27 and 34: 'a 2-benzothiazolyl radical.'
> Claims 28 and 35: 'a 5-phenyl-1, 3, 4-oxadiazolyl radical.'
> Claims 29 and 33: 'a 1-phenyl-5-tetrazolyl radical.'

Appellants stress that

* * * working examples (contained in their specification) describe the preparation and use of molecules which contain

25 different 5-pyrazolone photographic color coupler radicals and 30 different open-chain ketomethylene photographic color coupler radicals * * *

and that their

* * * disclosure of specific useful 'R' radicals includes 13 alkyl radicals, 1 cycloalkane radical, 8 aryl radicals, 122 heterocyclic radicals containing at least 1 nitrogen atom, 9 heterocyclic radicals containing at least 1 oxygen ****596** atom, and 17 heterocyclic radicals containing at least 1 sulfur atom.

The Board of Appeals recognized that appellants had disclosed a considerable number of examples of the various radicals in their specification, either directly by way of working examples or indirectly by way of incorporation by reference, but it nevertheless affirmed the sxaminer's rejection on this ground, noting that 'the application of the fundamental principle * * * ('that disclosure of a limited number of a large group of chemicals is not necessarily sufficient basis for broad claims even though appellant has made general reference to the group as a whole in his specification') 'is necessarily a matter of judgment based on the circumstances of each case'.' [FN12] While we agree with the quoted statement, we in turn note that our work would be immensely facilitated if the board (and the examiner, before a case reaches the board) would state the circumstances of the ***1401** case which have led it to judge that the limited number of chemicals specifically disclosed is not fairly representative of the large number of chemicals claimed. Specifically, if the board thought that appellants' working examples were deficient in some particular area or subclass embraced by the claim, there is no hint of that in its opinion.

> FN12. The bracketed quotation is from In re Oppenauer, 143 F.2d 974, 31 CCPA 1248 (1944); the terminal quotation is from Ex parte Heckert, 121 USPQ 587 (POBA 1958).

The solicitor has attempted to remedy this deficiency in the record by setting forth at great length in his brief the multitudes of specific chemicals covered by appellant's claims which are not included among their working examples. [FN13] However, the solicitor has not suggested that there is any evidence in the record that any significant number of these multitudes of specific chemicals would not be 'photographic color couplers capable of forming a dye and a mercaptan when reacted with oxidized aromatic primary amino color developing agent,' nor has he argued that any significant group of compounds embraced by the claims are so obviously inoperative that we can take judicial notice of the fact. While we appreciate that claims as broad as appellants' must necessarily read on many chemicals the operativeness of which the applicant has not individually verified, and while it might well have been reasonable in this case for the examiner or the board to have demanded specific proof from the appellants that this or that class of compounds embraced by the claims really could be used in the disclosed manner, we think the filing of the solicitor's brief is far too late a point in prosecution to inform an applicant of what additional working examples are thought to be needed to support his claims.

> FN13. For instance, we are informed that 'not counting stereoisomers,' the 20-carbon alkyl radical has 366,319 isomers, not all of which (or, to be fair, not a 'representative sampling' of which) are included in appellants' working examples and that, 'Among the more obvious radicals' which 'could be substituted for hydrogen at the 1-position' of the 5-pyrazolone nucleus, but which are not included in any of appellants' working examples, are 'amino, hydroxy, ester, carboxyl, sulfonyl per se, cycloalkyl, olefinic, actetylenic, heterocyclics, diazo, heavy metalcontaining, etc.'

In any event, as this court recently stated,

* * * there is no magical relation between the number of representative examples and the breadth of the claims; the number and variety of examples are irrelevant if the disclosure is 'enabling' and sets forth the 'best mode contemplated.' [FN14] (In re Borkowski, 422 F.2d 904, 910, 57 CCPA 946, 952 (1970).)

> FN14. No question has been raised in this case concerning satisfaction of the 'best mode' requirement.

Appellants have specifically disclosed how to make and use a large number of compounds and have asserted that other compounds, similar to the compounds specifically disclosed in certain stated respects, ***1402 **597** may be made and used in the same fashion. We see no reason, on the state of this record, to suspect that their assertion is not accurate or that appellants are not the pioneer inventors they claim to be. Appellant's application runs to 132 pages in the transcript of record, and we are not persuaded that any useful purpose would have been served by extending it with further working examples. See In re Kamal, 398 F.2d 867, 871, 55 CCPA 1409, 1413-1414 (1968).

The rejection of all claims as unsupported by the specification is accordingly reversed.

V. Does claim 25 fail to particularly point out and distinctly claim subject matter which appellants regard as their invention?

[4] Claim 24 recites that R in the formula COUP-S-R 'is a

phenyl radical incapable of forming a dye with said oxidized developing agent.' Claim 25 reads:

25. A photographic color coupler as described in claim 24 wherein the phenyl radical is a 3-octadecylcarbamylphenyl radical.

The examiner appears to have rejected claims 24, 25, and 30 (which is equivalent to claim 24 in this respect) on the ground that

Appellants' use of 'a phenyl' in claims 24, 25 and 30 involves a distortion of the term. The 'phenyl radical' means the radical derived from benzene by removing one hydrogen atom, and cannot include as appellant is using it, a radical derived from N-octadecylbenzamide (See claim 25). Compare In re Hill, (34 CCPA 1062, 161 F.2d 367) (1947).

The board affirmed only the rejection of claim 25 on this ground.

In re Hill, cited in the above quotation, held that a definition in the specification of a term used in a claim which distorts the common meaning of the term is not permissible and renders the claim in which the term appears indefinite. This court there affirmed a rejection because the term 'carbamide' was said by the Patent Office to mean the single substance urea whereas the claim used the phrase 'a carbamide formaldehyde resin' to mean one of a plurality of resins formed from formaldehyde and urea derivatives and substituted ureas as well as urea itself. The court found appellant had not established that such a meaning was proper.

The specification in this case attempts no definition of the claim language 'a phenyl radical.' Accordingly, we must presume that the phrase was used in its commonly accepted technical sense. Appellants apparently concede as much, arguing that their 'use of 'phenyl' in claim 25 is similar to referring to 'hydroxyphenyl',' which they assert is 'standard practice' citing Hackh's Chemical Distionary (3d ed. 1944). However, they have not referred us to any standard work on chemistry which indicates that the commonly accepted technical ***1403** meaning of the words 'a phenyl radical,' without more, would encompass the hydroxyphenyl radical, or any other radical the name of which includes the work 'phenyl.' On the contrary, Hackh's quite plainly defines 'phenyl' as 'The monovalent radical, C(6)H(5)--, derived from benzene, C(6)H(5), or phenol, C(6) H(5)OH.'

On the present record, therefore, we are faced with a claim for compounds containing a radical said simultaneously to be 'a phenyl' and 'a 3- octadecylcarbamylphenyl radical' and with the assertion of the Patent Office that the meaning of the phrase 'a phenyl radical' is 'confined to a single, definite radical' (to paraphrase the Hill case) not the 3-octadecylcarbamylphenyl radical, and we have been given no reason to doubt the Patent Office assertion. We therefore hold claim 25 indefinite and accordingly affirm its rejection under the second paragraph of 35 U.S.C. 112.

In summary, we affirm the rejection of claim 25 and reverse the rejection of claims 23, 24, 26-30, and 32-35.

Modified.

****598** ALMOND, Judge (dissenting), with whom BALDWIN, Judge, joins.

I respectfully disagree with the conclusion reached by the majority in part I of its opinion. Unlike the majority, I would affirm the rejection of all claims under 35 U.S.C. 112, second paragraph. In my opinion appellants have not overcome the contention of the Patent Office that the terms '5-pyrazolone coupler radical' and 'open-chain ketomethylene coupler radical' are indefinite. Since I also find myself in disagreement with some of what is said in parts II-V of the majority opinion, I would affirm the decision of the board on this ground alone and not reach the issues discussed by the majority in parts II-V.

As pointed out in the majority opinion, we have here a situation where the Patent Office contends that certain chemical terms are indefinite and appellants contend they are not. Based on two United States patents, cited by appellants for their use of the terms in question, and on two chemical texts which are not of record, the majority finds that the terms have a definite meaning to one of ordinary skill in the photographic art. In my opinion there is no real evidence of record to support this conclusion.

In regard to the two cited U.S. patents, I agree with the majority that 'these patents are not weighty evidence of the art recognition of the controverted terms,' since (1) there is no showing that the question of art recognition of the terms ever came up during the prosecution of these patent applications, and (2) both patents are assigned to the same assignee as the present application and were copending with the present application, which negates any presumption from the use of the terms in these patents that the terms are known to the art as a whole.

Since these two patents are not convincing of the art recognition of the controverted terms, there is no persuasive evidence before the court of the art recognition of those terms. The chemical texts cited in ***1404** the majority opinion cannot aid appellants in this case. These texts are not of record and the majority has quite properly refused to take judicial notice of them. By considering the texts anyway, the majority has clearly gone beyond that which is authorized by 35 U.S.C. 144, which requires that this court

'hear and determine * * * appeals on the evidence produced before the Patent Office.'

I think from the foregoing analysis that it is apparent that there remains the situation where one side argues that the terms are indefinite, the other side argues that they are not, and there is no persuasive evidence either way. Under the circumstances, I would place the burden on appellants to show that the terms in question have a definite art-recognized meaning. When an examiner rejects claims for indefiniteness under 112 in situations such as this, it seems to me he is really saying what the majority evidently would like to have seen more explicitly spelled out, i.e., that he thinks the use of the terms makes the claims indefinite and would like to see examples of their use in literature in the art. An examiner can do little more since it is nearly impossible as a practical matter to show that the terms are indefinite. That is, an examiner cannot cite patents, textbooks, dictionaries, etc. to show that the terms are indefinite since the mere absence of the terms from the reference materials means little and if the terms are present in the reference materials, it would indicate some art recognition unless, perchance, the terms are listed with the notation that they have no definite art-recognized meaning. On the other hand, the fact that the terms have a definite art-recognized meaning is much more easily shown. For example, literature references which use the terms can be cited, dictionary and encyclopedia definitions (such as those cited in the majority opinion) can be brought forth, and affidavits (such as the one tendered by appellants but not entered of record) can be submitted.

Therefore, when challenged as to the definiteness of the terms '5-pyrazolone **599 coupler radical' and 'open-chain ketomethylene coupler radical,' I think it was incumbent upon appellants to show that the terms do have an art-recognized meaning. This they have clearly failed to do. As noted previously, the only evidence of record tending to show the art recognition of the terms is found in the two U.S. patents which were cited by appellants, and the relevancy of these patents has been questioned by everyone including the majority. Since there is no other evidence of record to support appellants' position, I do not think it proper for the court to do for appellants (by finding reference to the terms in chemical texts) that which they should have done for themselves. To do so requires reliance on material which is clearly outside of the record in this case and which is not subject to being judicially noticed. This is not permissible under 35 U.S.C. 144.

For the foregoing reasons, I would affirm the decision of the board.

444 F.2d 588, 58 C.C.P.A. 1388, 170 U.S.P.Q. 330

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H

United States District Court,
D. Massachusetts.

BIOGEN, INC.,
v.
AMGEN, INC.

Civil Action No. 95-10496-RGS.

July 7, 1997.

Patentee brought action for infringement of patent for inducing production of human proteins in nonhuman host cells. Alleged infringer moved for summary adjudication of claim of patent. The District Court, Stearns, J., held that published abstract did not enable one skilled in the art to practice patent without undue experimentation.

Motion for summary adjudication denied.

West Headnotes

[1] Patents ⇐50.1
291k50.1 Most Cited Cases

Invention is not novel and is therefore unpatentable if invention was anticipated.

[2] Patents ⇐68
291k68 Most Cited Cases

To be a "printed publication" that anticipates patented invention, prior art reference must have been sufficiently accessible to the public interested in the art. 35 U.S.C.A. § 102.

[3] Patents ⇐69
291k69 Most Cited Cases

[3] Patents ⇐312(4)
291k312(4) Most Cited Cases

To establish anticipation of patented invention by printed publication, proponent must demonstrate by clear and convincing evidence that all of the elements and limitations of claim are expressly or inherently described within a single prior art reference and can therefore be reproduced by one skilled in the art without undue experimentation. 35 U.S.C.A. § 102(b).

[4] Patents ⇐57.1
291k57.1 Most Cited Cases

Extrinsic evidence may be considered to explain, but not to expand on, meaning of anticipatory reference to patented invention; specifically, court may look to extrinsic evidence to learn how person of ordinary skill would interpret anticipatory reference. 35 U.S.C.A. § 102(b).

[5] Patents ⇐70
291k70 Most Cited Cases

Abstract describing successful preparation of plasmid vector did not anticipate filing of application for patent for method of inducing production of human proteins in nonhuman "host" cells through use of recombinant deoxyribonucleic acid (DNA); abstract would not have enabled one of ordinary skill in the art to reproduce vector without undue experimentation. 35 U.S.C.A. § 102(b).

[6] Patents ⇐314(5)
291k314(5) Most Cited Cases

Whether making and using patented invention would have required undue experimentation, and thus whether disclosure is enabling, is a legal conclusion based upon several underlying factual inquiries, including quantity of experimentation necessary, amount of direction or guidance presented, presence or absence of working examples, nature of invention, state of prior art, relative skill of those in that art, and predictability or unpredictability of the art.

***40** John Sylvia, Patrick T. Clendenen, Mintz, Levin, Cohn, Ferris, Glovsky & Popeo, P.C., Boston, MA, James F. Haley, Kenneth B. Herman, Andrew S. Marks, Madge R. Kanter, Jane A. Massaro, Janis P. McLaughlin, Kathleen M. Walker, Fish & Neave, New York City, for Biogen, Inc.

Paul F. Ware, Eileen M. Herlihy, Goodwin, Procter & Hoar, Boston, MA, Karen J. Kramer, Lloyd R. Day, Jr., David M. Madrid, Robert M. Galvin, Ricardo Rodriguez, Gary H. Ritchey, Darren B. Mitchell, Karen A. Gibbs, Cooley Godward LLP, Palo Alto, CA, Steven M. Odre, Karol M. Pessin, Amgen, Inc., Thousand Oaks, CA, Vernon M. Winters, Cooley Godward LLP, San Francisco, CA, for Amgen, Inc.

MEMORANDUM AND ORDER ON AMGEN'S RENEWED MOTION FOR SUMMARY ADJUDICATION OF CLAIM 9 OF THE '702 PATENT

STEARNS, District Judge.

Biogen brought suit alleging among other wrongs that Amgen's product Neupogen (R) infringes claim 9 of U.S. Patent 4,874,702 (the " '702 patent"). [FN1] Amgen struck back with a counterclaim attacking the validity of claim 9. See 35 U.S.C. § 102(b). Amgen maintains that an abstract published by Glen Horn and Dr. Robert Wells in April of 1979 ("Horn & Wells 1979") anticipated the filing of the application for the '702 patent by more than a year. Biogen contends that there is a material dispute of fact whether or not Horn & Wells 1979 would have enabled one skilled in the art to replicate the invention disclosed in claim 9 without

undue experimentation.

FN1. Biogen's Complaint alleges that Amgen infringed on all claims of two of Biogen's patents, U.S. Patents 5,401,642 and 5,401,658, and claims 3, 7-9, 13 and 17 of the '702 patent. In a January 19, 1996 decision, the court dismissed all claims and counterclaims relating to the '702 patent except those involving claims 9 and 17.

***41** *BACKGROUND*

The '702 patent emanated from U.S. Patent Application Serial No. 921,803, which claims its earliest priority from British Application 8028983, filed on September 8, 1980, by two Belgian scientists, Walter Fiers and Erik Remaut. Biogen is the assignee of all rights under the '702 patent. The '702 patent discloses a method of inducing the production of human proteins in non- human "host" cells through the use of recombinant DNA. Claim 9 of the '702 patent discloses a technique for preparing a plasmid vector, pPLa23, a cloning tool that can be used to transfer genetic information from one organism into another. [FN2] Specifically Claim 9 of the '702 patent claims

FN2. A vector is a strand of DNA that can be inserted into a host cell where it will replicate itself. The "parent vector" identified by Fiers and Remaut in the '702 patent is pPLa23. Amgen asserts that for present purposes pPLa23 "is identical in all relevant respects" to the Horn & Wells 1979 vector, pRW601. Amgen's Memorandum in Support of Its Renewed Motion for Summary Adjudication, at 13. Biogen contends that claim 9 requires that the P subL promoter be capable of driving expression. Biogen also maintains that pRW601 is incapable of expression. Whether this is true or not (or is in fact a limitation of claim 9) is unnecessary to resolve given my ultimate conclusion that Horn & Wells 1979 is not enabling.

[a] recombinant DNA molecule comprising a vector according to Claim 1 and 2, and further comprising in one of said endonuclease recognition sites a DNA sequence coding for a eukaryotic, prokaryotic or viral protein, polypeptide, enzyme, hormone or antigen.

Claim 1 claims

> DNA downstream of the *Hae* III site at 73.1% of bacteriophage <<lambda>> in said DNA sequence.

Claim 2 claims: "[t]he vector of claim 1, having no active cro gene and no active N gene." [FN3]

FN3. Claim 9 depends from claims 1 and 2. The parties agree that a complete claims construction is unnecessary to resolve the present motion.

On March 1, 1979, Glen Horn, a graduate student at the University of Wisconsin, and his mentor, Dr. Robert Wells, published an abstract entitled "Cloning and Characterization of a 360 B.P. DNA Fragment Containing O subL of Phage <<lambda>>", *Federation Proceedings Abstracts,* Vol. 38, No. 3, at 298. [FN4] Horn & Wells 1979 describes the successful preparation of a plasmid vector, pRW601, which for present purposes is assumed to be identical to the vector disclosed by Fiers and Remaut in the '702 patent. [FN5]

FN4. Horn & Wells 1979 is a nine sentence abstract. Biogen claims that of the nine sentences, only two actually describe how Horn and Wells constructed plasmid vector pRW601.

FN5. Amgen claims that like the vector described in the '702 patent, the plasmid vector pRW601 described in Horn & Wells 1979:(1) contains the leftward promoter and operator region of phage, P subL O subL ; (2) contains an *Eco* RI site converted from the *Hae* III site at 73.1% of the DNA phage <<lambda>>; (3) contains a DNA sequence of phage << lambda>> DNA which extends no further than the *Hae* III site at 73.1% phage <<lambda>> and terminates at the same *Eco* RI site converted from a *Hae* III site disclosed in the Fiers and Remaut plasmid vector pPla23 and Figure 6 of the '702 patent; (4) lacks the cro gene; (5) lacks the N gene; (6) includes a DNA sequence known as "tet" downstream from P subL O subL ; and (7) contains two *Taq* I endonuclease recognition sites surrounding the tet r gene sequence. As in the '702 patent, one of the *Taq* I sites is located 26 basepairs downstream from the *Eco* RI site (converted from the *Hae* III site at 73.1% phage <<lambda>>). The second *Taq* I site is located 1270 basepairs downstream from the *Eco* RI site.

SUMMARY JUDGMENT

Summary judgment is appropriate when, based upon the pleadings, affidavits, and depositions, "there is no genuine issue as to any material fact, and [where] the moving party is entitled to judgment as a matter of law." [FN6] Fed.R.Civ.P. 56(c); *Gaskell v. Harvard Co-op. Society,* 3

F.3d 495, 497 (1st. Cir.1993). A dispute of fact is only genuine if there is sufficient evidence to permit a reasonable *42 jury to resolve the point in the nonmoving party's favor. *NASCO, Inc. v. Public Storage, Inc.*, 29 F.3d 28, 32 (1st Cir.1994). All reasonable inferences must be indulged in favor of the nonmoving party. *Oliver v. Digital Equipment Corp.*, 846 F.2d 103, 105 (1st Cir.1988).

FN6. A fact is considered material only when it has the "potential to affect the outcome of the suit under applicable law." *Nereida-Gonzalez v. Tirado-Delgado*, 990 F.2d 701, 703 (1st Cir.1993).

ANTICIPATION

[1][2][3][4] An invention is not novel and is therefore unpatentable if the invention was "anticipated." See *Shatterproof Glass Corp. v. Libbey-Owens Ford Co.*, 758 F.2d 613, 619 (Fed.Cir.1985). Anticipation of an invention is assumed if the invention was "described in a printed publication in this or a foreign country, ... more than one year prior to the date of the application for patent in the United States." 35 U.S.C. § 102(b). [FN7] To establish "anticipation" under § 102(b), the proponent must demonstrate by clear and convincing evidence that all of the elements and limitations of the claim are "expressly or inherently described" within a single prior art reference and can therefore be reproduced by one skilled in the art without "undue experimentation." [FN8] See *Ciba- Geigy Corp. v. Alza Corp.*, 864 F.Supp. 429, 434 (D.N.J.1994), *aff'd in part and vacated in part without op.*, 68 F.3d 487 (Fed.Cir.1995). See also *Tillotson, Ltd. v. Walbro Corp.*, 831 F.2d 1033, 1036 (Fed.Cir.1987). "Extrinsic evidence may be considered to explain, but not to expand on, the meaning of an anticipatory reference. Specifically, the [c]ourt may look to extrinsic evidence to learn how the person of ordinary skill would interpret an anticipatory reference." *Ciba-Geigy*, 864 F.Supp. at 436 (citations omitted).

FN7. To be a "printed publication" under § 102, a prior art reference must have been sufficiently accessible to the public interested in the art. *Constant v. Advanced Micro-Devices, Inc.*, 848 F.2d 1560, 1568 (Fed.Cir.1988). Biogen does not dispute that Horn & Wells 1979 is a "printed publication."

FN8. I agree with Biogen that *In re Sasse*, 629 F.2d 675, 681 (C.C.P.A.1980), to the extent that it can be read to imply that prior art references are presumed to be enabling, has no relevance to the facts of this case.

DISCUSSION

Does Horn & Wells 1979 Enable One Skilled in the Art to Reproduce pRW601 Without Undue Experimentation? One Skilled in the Art

[5] Biogen maintains that Horn & Wells 1979 did not anticipate claim 9 of the '702 patent because it would not have enabled one of ordinary skill in the art to reproduce pRW601 without undue experimentation. Biogen argues that Horn & Wells 1979 is an abstract, not a recipe, and thus lacks the critical information necessary to guide a skilled practitioner working in a 1979 molecular biology laboratory.

The first task is to determine the 1979 genus of one of ordinary skill in the art of plasmid vector preparation and the recombinant DNA technique of promoting expression. In *Custom Accessories v. Jeffrey-Allan Industries*, 807 F.2d 955 (Fed.Cir.1986), the Federal Circuit taught that

> [t]he person of ordinary skill is a hypothetical person who is presumed to be aware of all the pertinent prior art. The actual inventor's skill is not determinative. Factors that may be considered in determining level of skill include: type of problems encountered in art; prior art solutions to those problems; rapidity with which innovations are made; sophistication of the technology; and educational level of active workers in the field. Not all such factors may be present in every case, and one or more of them may predominate.

Id. at 962-963 (citations omitted).

Amgen initially identified a laboratory technician working in the field of plasmid vector preparation as the template for a skilled practitioner in the art of recombinant DNA in 1979. Amgen's Statement of Undisputed Facts ¶ 15, *citing* Second Chamberlin Decl. ¶ 85. At the hearing on its motion, however, Amgen agreed with the opinion of Biogen's expert, Dr. Nikos Panayotatos, that a laboratory technician in 1979 would not have been able to prepare a pRW601 vector without the benefit of a detailed protocol and knowledgeable supervision. See February 26, 1997 Tr. at 8-11; Panayotatos Decl. ¶ 13-16.

*43 I conclude that Dr. Horn, the co-author of the abstract, is a more appropriate exemplar of one with ordinary skill in the art of recombinant DNA at the relevant time. It is somewhat unlikely that a mere technician in 1979 would have had any extensive familiarity with the literature in what then was an emerging science. Dr. Horn, on the other hand, as a graduate student working under Dr. Wells, would have had a relatively sophisticated grasp of the field. See Wells Decl. ¶ 5. The work underlying his dissertation, which involved the isolation, characterization and analysis of the pRW601 segment of <<lambda>> phage DNA, would also have tutored him in the techniques of DNA fragment separation and manipulation known to the art in

1979.

Undue Experimentation

[6] As said before, to "anticipate" an invention, the prior art reference must enable one skilled in the art to reproduce the invention described in the patent without "undue experimentation." "Whether making and using the invention would have required undue experimentation, and thus whether the disclosure is enabling, is a legal conclusion based upon several underlying factual inquiries." *Genentech, Inc. v. Novo Nordisk, A/S,* 108 F.3d 1361, 1365 (Fed.Cir.1997) (citation omitted). The factors to be considered in determining whether or not experimentation is undue are "the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, [and] the predictability or unpredictability of the art." *Ex parte Formal,* 230 USPQ 546, 547 (Bd.Pat.App.Inter.1986). "That *some* experimentation is required is not fatal; the issue is whether the amount of experimentation required is 'undue.' " *In re Vaeck,* 947 F.2d 488, 495 (Fed.Cir.1991).

The Disclosures of Horn & Wells 1979

I propose to evaluate each of the disclosures of Horn & Wells 1979 in light of the standards described above, keeping in mind that the issue is the enablement of one skilled in the art in 1979.

"A Hae III digest of a segment of <<lambda>> DNA was first fractionated by RPC-5 column chromatography."

That the theory and practice of accomplishing a digest using *Hae* III restriction enzyme were a matter of common knowledge to a practitioner of the art in 1979 is not disputed. Because the details of RPC-5 column chromatography were published in 1976, a person skilled in the art (as defined) would have been familiar with the column chromatography method of DNA fragment separation in 1979. See Hardies & Wells, *Proceedings from the National Academy of Sciences USA,* Vol. 73, at 3117-3121.

What Horn & Wells 1979 does not, however, disclose is the identity of the "segment" of <<lambda>> phage DNA that was subjected to the *Hae* III digest. Thus, a skilled practitioner in 1979 would have had to isolate the desired 352 basepair fragment [FN9] from the entire 48,000 basepairs of <<lambda>> phage DNA. The magnitude of this task is made clear by Dr. Horn in his Ph.D. dissertation.

> FN9. The parties agree that Horn & Wells 1979's identification of the desired fragment as containing 360 rather than 352 basepairs is immaterial.

> The cloning [of the 352 basepair *Hae* III fragment containing the P subL O subL sequence] required the initial partial purification of the P subL fragment away from most other <<lambda>> *Hae* III fragments. This was accomplished by RPC-5 fractionation of the *Hae* III digest of a plasmid containing only a portion of the lambda genome. Thus, the frequency of insertion of the desired P subL fragment was high enough to allow direct screening of all inserted plasmids. One-fourth of all cloned plasmids had picked up an inserted fragment, and approximately one-third of these had inserted the P subL fragment. The P subL fragment was identified by restriction mapping, sequencing, operator function, and promoter location.

Horn Ph.D. dissertation, at 11-15, ¶ 1.

> Since the desired fragment represents less than 1% of the lambda genome, the insertion frequency of 352-P subL was increased by ***44** first partially purifying it away from the other lambda *Hae* III fragments.

Id. at 11-10, ¶ 1.

It follows that the probability of isolating and cloning the desired 352 basepair fragment on any given attempt using the entire <<lambda>> Phage genome would have been considerably less than 0.1%, even if all of the technical procedures were 100% successful. [FN10]

> FN10. There is evidence that Dr. Horn required nineteen months to achieve the result reported in Horn & Wells 1979.

"The partially purified O subL fragment was then ligated into the Eco RI site of pBR322 and cloned in E. coli C600 (R- M- recBC +) using a technique which converts the Hae III ends of the fragment into Eco RI sites."

It is unclear what Horn & Wells 1979 meant by a "partially purified" O subL fragment. (How mary other *Hae* III fragments in addition to the 352 basepair fragment of interest were present in the DNA mixture used for ligation into pBR322?). How Horn and Wells determined that the fragment used for ligation into pBR322 contained the O subL sequence is also unclear.

Assuming the successful isolation of the desired fragment, a skilled practitioner in the art in 1979 could have prepared an *Eco* RI-digested pBR322 plasmid for ligation, as it is undisputed that the technique of blunt-end DNA ligation was well known to molecular biologists in 1979. However, there is no description of the specific "technique" used by Horn and Wells to convert the *Hae* III ends to *Eco* RI sites prior to ligation. Moreover, a practitioner might have found the wording of the abstract confusing because the modification used by Horn to allow blunt-end ligation of the

Hae III fragments within an *Eco* RI site in pBR322 requires the enzymatic alteration of the *Eco* RI sites, not the *Hae* III sites as Horn & Wells 1979 implies.

"At least six single inserts and one double insert of this fragment were characterized."

The method used by Horn and Wells to "characterize" the *Hae* III fragment is not disclosed. Assuming that the clones were analyzed by *Eco* RI digestion and partial sequence analysis, a skilled practitioner in 1979 would have had no guidance in distinguishing the clone containing the 352 basepair fragment of interest from the remaining clones possessing incorrect or "contaminating" *Hae* III fragments.

"All have two EcoRI sites and have the P subL promoter(s) pointing toward the tet r genes of the vector."

Assuming that the practitioner was able to accomplish separation analysis of the fragments resulting from the *Eco* RI digestion, he or she could have performed an *Eco* RI digestion of the clone(s) to determine the presence of the two *Eco* RI sites. There is, however, no indication of how the presence and direction of the P subL promoter(s) was determined.

"EcoRI digestion of the single insert plasmid (pRW601) followed by sucrose gradient centrifugation separated the 360 b.p. fragment from the vector "

That a person of ordinary skill in the art in 1979 could have performed an *Eco* RI digestion of pRW601 is not disputed. The technical details of sucrose gradient centrifugation were known to the art in 1979 and thus available to a technician with the requisite skill. See Hardies & Wells, *Gene,* Vol. 7, at 1- 14.

"DNA sequencing on the half of the fragment 'upstream' from the P subL transcript reveals an unusually large A-T rich segment"

The technical details of DNA sequencing were in the public domain in 1979, and thus a person of ordinary skill in the art would have been able to partially sequence the cloned *Hae* III fragment. See Maxam & Gilbert, *Proceedings from the National Academy of Sciences USA,* Vol. 74, at 560-564.

SUMMARY

It follows that most of the steps set out in Horn & Wells 1979 were within the capacity of a person skilled in the art in 1979. However, the critical missing element is the (probably deliberate) failure of Horn and Wells to disclose their starting segment of <<lambda>> DNA. The <<lambda>> phage genome has 148 *Hae* III *45 sites. When digested with *Hae* III, the 48,000 basepair >>> DNA string is cut at each of those sites. Thus, the digestion produces 149 separate fragments. Of these 149 fragments, seventeen are in the 310-410 basepair range. Because the RPC-5 column chromatography method identified in Horn & Wells 1979 was incapable of separating these seventeen fragments, a person of ordinary skill in the art in 1979 would have faced the intimidating task of seeking the basepair fragment described in the abstract by trial and error. See Panayotatos Decl. ¶¶ 19-22. [FN11] Equally daunting, Horn and Wells sequenced only half of the cloned DNA fragment. Consequently, a skilled practitioner, even if he or she believed that the correct starting segment of <<lambda>> phage DNA had been isolated, would have had difficulty discerning that the completed vector lacked the cro gene and the N gene as required by claim 2.

> FN11. Amgen argues that in 1979 there were two "common knowledge" techniques for isolating DNA fragments for cloning: (1) nitrocellulose filter binding; and (2) gel electrophoresis. Biogen counters that nitrocellulose filter binding was not a known technique in 1979 for isolating DNA fragments and that gel electrophoresis cannot isolate the Horn & Wells 1979 *Hae* III fragment from the sixteen other similarly sized *Hae* III fragments in <<lambda>> phage DNA.

Amgen more or less concedes the omissions in Horn & Wells 1979, [FN12] but argues that a skilled practitioner would have compensated for the lack of concrete direction by resorting to his or her knowledge of the art. For example, Amgen maintains that a practitioner could have used gel electrophoresis to isolate a *Hae* III fragment containing a P subL O subL promoter by relying on the "teaching" of an article published by Zafri Humayan and his colleagues in 1977, "Completed DNA Sequences and Organization of Repressor-binding Sites in the Operators of Phage Lambda," *Journal of Molecular Biology, Vol.* 112, at 265-277. Amgen contends that Humayan isolated a precursor of the Horn & Wells 1979 *Hae* III segment using gel electrophoresis. Putting aside Biogen's argument that Humayan's "*Hae* 340" preparation most likely contained all of the seventeen Doppelganger fragments, see Biogen's Response to Amgen's Supplemental Submission, at 9, Amgen's attempt to bridge the critical gap in Horn & Wells 1979 unacceptably expands on the "known in the art" doctrine. The Federal Circuit's discussion in *Genentech,* 108 F.3d at 1366, is worth quoting at length.

> FN12. Amgen specifically concedes that a person skilled in the art would not have known the segment of <<lambda>> DNA with which Horn and Wells had started and would as a result have had to digest the entire phage <<lambda>> >

> genome with *Hae* III. Amgen also agrees that the practitioner would have faced the problem of separating the desired *Hae* III fragment from the 149 *Hae* III fragments produced by the digest. Amgen's Reply Memorandum, at 14-15.

It is true, as Genentech argues, that a specification need not disclose what is well known in the art. See, e.g., *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed.Cir.1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. This specification provides only a starting point, a direction for further research.

While I conclude that a practitioner skilled in the art could have prepared the pRW601 vector by bridging the gaps in Horn & Wells 1979 with inspired recourse to the existing literature, [FN13] for the reasons stated, I also conclude that Amgen has failed to meet its ***46** burden of showing by clear and convincing evidence that this feat could have been achieved without undue experimentation.

> FN13. The Declaration of Dr. Keith Backman is the most persuasive of Amgen's submissions on this point. I do note that Dr. Backman was forced to turn to Dr. Horn's later published Ph.D. thesis to confirm his deduction as to how Horn was able to verify that the *Hae* III fragment contained the leftward promoter and operator region of <<lambda>> DNA. Backman Decl. ¶ 18.

ORDER

For the foregoing reasons, Amgen's Motion for Summary Adjudication of Claim 9 of the '702 patent is *DENIED.*

SO ORDERED.

973 F.Supp. 39

END OF DOCUMENT

United States Court of Appeals,
Federal Circuit.

ELAN PHARMACEUTICALS, INC., and Athena Neurosciences, Inc., Plaintiffs-Appellants,
v.
MAYO FOUNDATION FOR MEDICAL EDUCATION AND RESEARCH, Defendant-Appellee.

No. 00-1467.

DECIDED: Aug. 30, 2002.

Patentee brought action against alleged infringer relating to patent that disclosed "recipe" for producing transgenic mice. The United States District Court for the Northern District of California, William H. Alsup, J., granted summary judgment for alleged infringer, 175 F.Supp.2d 1209. Patentee appealed. Superceding its prior opinion, 243 F.3d 567, the Court of Appeals, Pauline Newman, Circuit Judge, held that patent claim was not anticipated.

Reversed and remanded.

Dyk, Circuit Judge, filed a dissenting opinion.

West Headnotes

[1] Patents ⇐314(5)
291k314(5) Most Cited Cases

In patent law, anticipation is a question of fact, as is the question of inherency. 35 U.S.C.A. §§ 101, 102(a, e), 103.

[2] Patents ⇐72(1)
291k72(1) Most Cited Cases

Proof of anticipation differs from that for obviousness in that prior knowledge by others requires that all of the elements and limitations of the claimed subject matter must be expressly or inherently described in a single prior art reference; the single reference must describe and enable the claimed invention, including all claim limitations, with sufficient clarity and detail to establish that the subject matter already existed in the prior art and that its existence was recognized by persons of ordinary skill in the field of the invention. 35 U.S.C.A. §§ 101, 102(a, e), 103.

[3] Patents ⇐50.1
291k50.1 Most Cited Cases

To be patented an invention must be new; if it is not new, that is, if it was known to others, it is said to be " 35 U.S.C.A. §§ 101, 102(a, e).

[4] Patents ⇐72(1)
291k72(1) Most Cited Cases

An anticipating reference must disclose every element of the challenged patent claim and enable one skilled in the art to make the anticipating subject matter. 35 U.S.C.A. §§ 101, 102(a, e), 103.

[5] Patents ⇐65
291k65 Most Cited Cases

[5] Patents ⇐69
291k69 Most Cited Cases

When anticipation is based on inherency of patent limitations not expressly disclosed in the assertedly anticipating reference, it must be shown that the undisclosed information was known to be present in the subject matter of the reference. 35 U.S.C.A. §§ 101, 102(a, e), 103.

[6] Patents ⇐65
291k65 Most Cited Cases

An inherent patent limitation is one that is necessarily present; invalidation based on inherency is not established by probabilities or possibilities. 35 U.S.C.A. §§ 101, 102(a, e), 103.

[7] Patents ⇐66(1.25)
291k66(1.25) Most Cited Cases

General instructions to conduct failure-prone activities, such as gene transfer between humans and animals, and ensuing uncertainties with respect to gene expression and enzymatic cleavage of mutated human protein with animal enzymes, did not meet the legal criteria of "anticipation" of a successful product of transgenic activity; general recitation of known procedures in prior art, none of which was carried out by prior inventor, did not defeat "novelty" of specific mouse that was actually produced by patentee. 35 U.S.C.A. §§ 101, 102(a, e), 103.

[8] Patents ⇐57.1
291k57.1 Most Cited Cases

In patent law, inherency cannot be based on the knowledge of the inventor; facts asserted to be inherent in the prior art must be shown by evidence from the prior art.

[9] Patents ⇐51(1)
291k51(1) Most Cited Cases

Purpose of the patent law's rule of inherency is to accommodate common knowledge, knowledge that judges

might not know but that would be known to practitioners in the field.

[10] Patents ⇐51(2)
291k51(2) Most Cited Cases

New products are not anticipated when they did not previously exist, whether or not the process for making them is generally known.

[11] Patents ⇐51(3)
291k51(3) Most Cited Cases

"Anticipation" in the patent sense means that the subject matter was previously known; a precatory suggestion of general procedures that may or may not succeed in producing the novel product does not convert the suggested product into a previously existing product. 35 U.S.C.A. §§ 101, 102(a, e).

[12] Patents ⇐16.5(1)
291k16.5(1) Most Cited Cases

[12] Patents ⇐50.1
291k50.1 Most Cited Cases

Patentability requires novelty and unobviousness in light of the prior art, not in light of what the inventor knew and included in his patent application; anticipation is the epitome of obviousness, and both are measured by what was previously known to persons in the field of the invention, as discussed in precedent. 35 U.S.C.A. §§ 101, 102(a, e), 103.

Patents ⇐328(2)
291k328(2) Most Cited Cases

5,441,870. Cited.

Patents ⇐328(2)
291k328(2) Most Cited Cases

5,612,486, 5,850,003. Construed.
***1223** Lynn H. Pasahow, Fenwick & West LLP, of Palo Alto, California, argued for plaintiffs-appellants. Of counsel on the brief were Beth H. Parker, Mary T. Huser, and S. Christian Platt, McCutchen, Doyle, Brown & Enersen, LLP, of Palo Alto, California. Of counsel was Thomas S. Hixson, McCutchen, Doyle, Brown & Enersen, LLP, of San Francisco, California.

Robert E. Hillman, Fish & Richardson, P.C., of Boston, Massachusetts, argued for defendant-appellee. Of counsel were Shelley K. Wessels, Karen I. Boyd, and Curtis MacFerrin, Fish & Richardson, P.C., of Menlo Park, California. Also of counsel was Chad A. Hanson, Fish & Richardson, P.C., of Minneapolis, Minnesota.

Before NEWMAN, GAJARSA, and DYK, Circuit Judges.

Opinion for the court filed by Circuit Judge PAULINE NEWMAN. Dissenting opinion filed by Circuit Judge DYK.

PAULINE NEWMAN, Circuit Judge.

Elan Pharmaceuticals, Inc. and Athena Neurosciences, Inc. (collectively "Elan") appeal the decision of the United States District Court for the Northern District of California, granting summary judgment in favor of the Mayo Foundation for Medical Education and Research ("Mayo"). [FN1] The district court held that Elan's two patents in suit, United States Patent No. 5,612,486 for "Transgenic Animals Harboring APP Allele Having Swedish Mutation" (the '486 patent) and continuation Patent No. 5,850,003 for "Transgenic Rodents Harboring APP Allele Having Swedish Mutation" (the '003 patent), inventors Lisa McConlogue and Jun Zhao, are invalid on the ground of anticipation by United States Patent No. 5,455,169 for "Nucleic Acids for Diagnosing and Modeling Alzheimer's Disease" (the Mullan patent). We reverse the summary judgment, for the legal requirements of anticipation were not met on the facts of record, and remand for further proceedings.

> FN1. *Elan Pharmaceuticals, Inc. v. Mayo Foundation for Medical Education & Research,* 175 F.Supp.2d 1209 (N.D.Cal.2000).

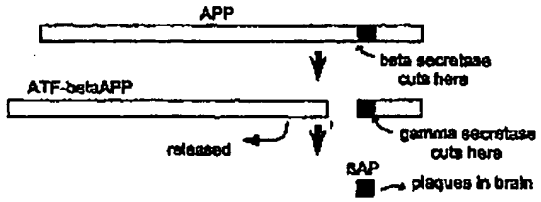
BACKGROUND

Alzheimer's disease is a progressive neurodegenerative disease that primarily afflicts the elderly. Elan's '486 and '003 patents are directed to transgenic animals ***1224** whose genetic makeup has been altered so that they are susceptible to Alzheimer's disease. The DNA of these animals has been modified to contain a mutated human gene called the "Swedish mutation," for the gene was isolated from the cells of a Swedish family having an unusually high incidence of early-onset Alzheimer's disease. [FN2]

> FN2. A gene is a segment of DNA. A mutation is a change in a gene and the resulting change in a protein produced by the gene. A gene produces a protein by first copying (transcribing) a portion of DNA into an intermediate strand designated mRNA; the mRNA then produces, through several complex steps, the sequence of amino acids that constitutes the protein. This procedure is called "gene expression." *See* Bruce Alberts et al., *Essential Cell Biology* (1998), Ch.6 "DNA," Ch.7 "From DNA to Protein."

The brains of people with Alzheimer's disease contain abnormal tangles and deposits of plaques. At the time of these Elan inventions it was known that a principal component of these plaques is a protein fragment called beta-amyloid peptide (betaAP, also designated ?AP and A?). The presence of betaAP in the brain is believed to induce or foster formation of the Alzheimer's plaques. It was known that betaAP may be formed when a protein produced in the brain, called the amyloid precursor protein (APP), is cleaved by enzymes in the brain. The Elan patents summarize scientific research in this field, including various reported mutations. Elan explains that an enzyme called beta-secretase cuts the APP molecule between amino acids 596 and 597, releasing a larger protein fragment called the amino terminal fragment (ATF-betaAPP); and an enzyme called gamma-secretase releases the smaller betaAP fragment from the remaining portion of the APP. This mechanism is illustrated in the Elan brief as follows:

Fig.1 - Processing of APP to ßAP and ATF-betaAPP



Humans who do not develop Alzheimer's disease are believed to break down APP in a manner that does not produce significant amounts of betaAP.

The Prior Art

The prior art on which the district court based its summary judgment of anticipation is the Mullan patent. Dr. Mullan had learned of the Swedish family susceptible to Alzheimer's disease, obtained samples of their DNA, isolated the relevant mutated gene, and identified the nature and location of the mutation in the gene as well as in the mutated protein (APPsw) expressed by the gene. Mullan explained that in the Swedish mutation the DNA nucleotides that encode codons 670 and 671 [FN3] replace lysine and methionine, the amino acids normally encoded at these positions, with asparagine and leucine. Mullan states that transgenic animals containing the mutated ***1225** gene can be used in Alzheimer's disease (AD) research and therapy:

> FN3. The mutation positions at codons 670/671 (Mullan) and 596/597 (Elan) are the same, due to differing starting points in the APP chain. *See* '486 patent, col. 11, lines 29-34.

> The invention also provides a transgenic non-human animal containing, in a germ or somatic cell, the mutated nucleic acid of the invention, wherein the animal expresses a human amyloid precursor protein or fragment thereof which encodes an amino acid other than lysine at codon 670 and/or an amino acid other than methionine at codon 671.
>
> * * * * * *
>
> The invention also provides a method of screening for an agent capable of treating AD. The method comprises contacting these transgenic animals or host cell lines with the agent and monitoring the expression, processing or deposition of amyloid precursor protein or fragments thereof.

Mullan, col. 4, lines 36-64. Mullan states that the mutated human gene can be used to create transgenic animals in various ways; for example:

> In yet a further use of the present invention, the mutated gene (*i.e.*, a variant APP codon 670/1 gene) can be excised for use in the creation of transgenic animals containing the mutated gene. For example, an entire human variant APP codon 670/1 allele can be cloned and isolated, either in parts or as a whole, in a suitable cloning vector (*e.g.*, 1Charon35, cosmid, retrovirus or yeast artificial chromosome). The vector is selected based on the size of the desired insert and the ability to produce stable chromosome integration.

Col. 11, lines 23-31. Mullan also states that the mutated gene can be transferred to a mouse that preferably will express the variant human APP:

> The human variant APP codon 670/1 gene, either in parts or in whole, can be transferred to a host non-human animal, such as a mouse. As a result of the transfer, the resultant transgenic non-human animal will express one or more variant APP codon 670/1 polypeptides. Preferably, a transgenic non-human animal of the invention will express one or more variant APP codon 670/1 polypeptides in a neuron-specific manner (Wirak et al. (1991) EMBO 10:289). This may be accomplished by transferring substantially the entire human APP gene (encoding a codon 670/1 mutant) including the 4.5 kilobase sequence that is adjacent to and upstream of the first major APP transcriptional start site.

Col. 11, lines 32-43. Mullan discusses the various known procedures of gene transfer, citing scientific articles as to each "approach" used to create transgenic animals:

> One approach to creating transgenic animals is to target a mutation to the desired gene by homologous recombination in an embryonic stem (ES) cell line in vitro followed by microinjection of the modified ES cell line into a host blastocyst and subsequent incubation in a foster mother (see Frohman and Martin, Cell (1989) 56:145). Alternatively, the technique of microinjection of the mutated gene, or a portion thereof, into a one-cell embryo followed by incubation in a foster mother can be used. Certain possibilities for the general use of

transgenic animals, particularly transgenic animals that express a wild-type APP fragment, are disclosed in Wirak et al., the EMBO Journal, 10(2) 289-296 (1991); Schilling et al., Gene 98(2) 225-230 (1991); Quon, et al. (1991) Nature 352:239; Wirak, et al. (1991) Science 253:323; and Kawabata, et al. (1991) Nature 354:476. Alternatively, viral vectors, *e.g.*, Adeno-associated virus, can be used to deliver the mutated gene to the stem cell. In addition, such viral vectors can be used to deliver the mutated gene to a developed animal and ***1226** then used to screen (Mendelson et al. Virology 166:154-165; Wondisford et al. (1988) Molec. Endocrinol. 2:32-39 (1988)).

Col. 11, line 58 to col. 12, line 11. Mullan also states that the mouse gene allele can be mutated to produce a mutation corresponding to the Swedish mutation:

Site-directed mutagenesis and/or gene conversion can also be used to mutate a murine APP gene allele, either endogenous or transfected, such that the mutated allele does not encode lysine/methionine at the codon position in the mouse APP gene that corresponds to codon 670/1 (of APP770) of the human APP gene (such position is readily identified by homology matching of the murine APP gene or APP protein to the human APP gene or APP770 protein). Preferably, such a mutated murine allele would encode asparagine or leucine at the corresponding codon position.

Col. 12, lines 12-21.

It is undisputed that Mullan did not produce a transgenic animal with the Swedish mutation, or determine which of the known procedures would be effective for this purpose, or suggest conditions or details of any method for successful production of the desired animal. Expert witnesses for both sides testified as to the difficulty, uncertainty, unpredictability, and low success rate of each method that has been used to create transgenic animals.

The Elan Patents

The Elan patents describe the production and characteristics of transgenic rodents, specifically mice, whose DNA contains a gene harboring the Swedish mutation, which gene expresses human APP having the Swedish mutation. This APPsw in turn produces human betaAP by action of the mouse enzymes. Expert witnesses for both sides testified as to the unpredictability of the process and the various steps thereof, for not all of the known methods may work, very few attempted gene transfers are successful, and of the relatively few mice that may accept the Swedish gene, not all will express the mutated human APP in a way that is subject to enzymatic cleavage to produce betaAP.

Elan explains that the production of betaAP in the mouse brain is difficult to detect because the betaAP molecule is relatively small. The Elan patents report detecting the betaAP by detecting the larger cleavage fragment, ATF-betaAPP. Claim 1 of the '486 patent includes this limitation:

1. A transgenic rodent comprising
a diploid genome comprising a transgene encoding a heterologous APP polypeptide having the Swedish mutation wherein the amino acid residues at positions corresponding to positions 595 and 596 in human APP695 are asparagine and leucine, respectively,
wherein the transgene is expressed to produce a human APP polypeptide having the Swedish mutation,
and wherein said polypeptide is processed to ATF-betaAPP in a sufficient amount to be detectable in a brain homogenate of said transgenic rodent.

The '003 patent differs from the '486 patent in that the '003 claims include a promoter and a polyadenylation site. Claim 1 of the '003 patent follows:

1. A transgenic rodent comprising
a diploid genome comprising a transgene comprising in operable linkage a promoter, a DNA segment encoding a heterologous APP polypeptide and a polyadenlyation site, wherein the APP polypeptide has the Swedish mutation whereby the amino ***1227** acid residues at positions corresponding to positions 595 and 596 in human APP695 are asparagine and leucine, respectively,
wherein the transgene is expressed to produce a human APP polypeptide having the Swedish mutation,
and wherein said polypeptide is processed to ATF-betaAPP in a sufficient amount to be detectable in a brain homogenate of said transgenic rodent.

For both patents, dependent claims 2 and 3 add the limitations that the rodent is murine (mouse) and that the transgene is nonhomologously integrated. These limitations are not asserted to add patentable distinctions. Elan concentrates on the '486 patent on this appeal.

The Mullan patent was prior art based on its filing date, and the examiner granted the Elan patents only after Elan added the final clause to the claims. Elan argues on this appeal that its claims are limited by the presence of detectable ATF-betaAPP in the rodent brain, that this limitation is not shown by Mullan, and thus that as a matter of law the claims cannot be "anticipated." Elan states that "ATF-betaAPP was not even disclosed in humans until after Mullan was filed," and thus that this limitation cannot be deemed "inherent" in the Mullan disclosure.

The district court found that although Mullan does not mention the formation of ATF-betaAPP, its formation is inherent in Mullan's general teachings of transgenic mice with the Swedish mutation. The court found that the Elan claims do not require that the claimed mice be tested for detectable ATF- betaAPP in brain homogenate. Thus the court found that Mullan anticipates the Elan claims, and on summary judgment held the claims of both patents invalid

on this ground.

DISCUSSION

The grant of summary judgment on a question of fact requires that "when the facts are viewed in the light most favorable to the non-moving party and all doubts are resolved in favor of the non-movant, there are no genuine issues of material fact and the moving party is entitled to judgment as a matter of law." *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 247-48, 106 S.Ct. 2505, 91 L.Ed.2d 202 (1986). Elan argues that the factual and legal criteria of anticipation were not met. Elan also argues that summary judgment was inappropriate because material facts were in dispute, and that Elan would prevail if the disputed facts were resolved in its favor.

A

[1][2][3] To be patented an invention must be new. 35 U.S.C. §§ 101, 102(a), (e). If it is not new, that is, if it was known to others, it is said to be "anticipated." *Hoover Group, Inc. v. Custom Metalcraft, Inc.*, 66 F.3d 299, 302, 36 USPQ2d 1101, 1103 (Fed.Cir.1995) ("lack of novelty (often called 'anticipation') requires that the same invention, including each element and limitation of the claims, was known or used by others before it was invented by the patentee"). Anticipation is a question of fact, as is the question of inherency. *In re Schreiber*, 128 F.3d 1473, 1477, 44 USPQ2d 1429, 1431 (Fed.Cir.1997). Its proof differs from that for obviousness, 35 U.S.C. § 103, in that prior knowledge by others requires that all of the elements and limitations of the claimed subject matter must be expressly or inherently described in a single prior art reference. *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950 (Fed.Cir.1999); *Constant v. Advanced Micro-Devices, Inc.*, 848 F.2d 1560, 1571, 7 USPQ2d 1057, 1064 (Fed.Cir.1988). The single reference must describe and enable the claimed invention, ***1228** including all claim limitations, with sufficient clarity and detail to establish that the subject matter already existed in the prior art and that its existence was recognized by persons of ordinary skill in the field of the invention. *Crown Operations International, Ltd. v. Solutia Inc.*, 289 F.3d 1367, 1375, 62 USPQ2d 1917, 1921 (Fed.Cir.2002); *In re Spada*, 911 F.2d 705, 708, 15 USPQ2d 1655, 1657 (Fed.Cir.1990) ("the reference must describe the applicant's claimed invention sufficiently to have placed a person of ordinary skill in the field of the invention in possession of it").

[4][5][6] The anticipating reference "must disclose every element of the challenged claim and enable one skilled in the art to make the anticipating subject matter." *PPG Industries, Inc. v. Guardian Industries Corp.*, 75 F.3d 1558, 1566, 37 USPQ2d 1618, 1624 (Fed.Cir.1996). When anticipation is based on inherency of limitations not expressly disclosed in the assertedly anticipating reference, it must be shown that the undisclosed information was known to be present in the subject matter of the reference. *Continental Can Co. USA, Inc. v. Monsanto Co.*, 948 F.2d 1264, 1269, 20 USPQ2d 1746, 1749-50 (Fed.Cir.1991). An inherent limitation is one that is necessarily present; invalidation based on inherency is not established by "probabilities or possibilities." *Scaltech, Inc. v. Retec/Tetra, LLC.*, 178 F.3d 1378, 1384, 51 USPQ2d 1055, 1059 (Fed.Cir.1999).

B

The district court found that the Elan claims were anticipated by Mullan because use of the standard procedures set forth in Mullan would be expected to produce a statistically small percentage of transgenic mice, and some of these mice would be expected to produce detectable ATF-betaAPP on enzymatic cleavage. The court deemed it irrelevant that the ATF-betaAPP was not described in the prior art. The court found that since the low success rate for gene transfer and expression was known, it was a matter of statistical probability that a few successful results would be obtained. Thus the district court found that the Elan invention was anticipated by Mullan.

[7] Elan argues that Mullan does no more than teach broad known "recipes" for gene transfer, and that the Mullan disclosure is simply an invitation to experiment, with no assurance of success. That is clearly so. Although Mullan described known procedures for making a transgenic animal, he neither described every element of the claims, nor taught, in terms other than by trial and error and hope, production of a transgenic mouse having detectable ATF-betaAPP in brain homogenate. General instructions to conduct such failure-prone activities as gene transfer between humans and animals, and the ensuing uncertainties with respect to gene expression and enzymatic cleavage of the mutated human protein with animal enzymes, do not meet the legal criteria of "anticipation" of the successful product of transgenic activity. A general recitation of known procedures, none of which was carried out by Mullan, does not defeat the "novelty" of the specific mouse that was actually produced by Elan. [FN4]

> FN4. In support of its argument on the uncertainty and difficulty of producing a successful transgenic mouse using known general procedures, Elan points out that the accused Mayo mouse was the 2,576th mouse that was screened.

Elan states that the concluding clause of its claims, the processing of the human APPsw to form detectable ATF-betaAPP in the rodent brain, is the "key element" of the claims. Elan stresses that the patent examiner required the inclusion of this limitation ***1229** in order to distinguish

the Mullan reference, for Mullan does not mention producing detectable ATF-betaAPP or its use as a proxy for detecting the smaller betaAP molecule. Elan argues that detection of the ATF-betaAPP permits determination of when the Swedish DNA has been successfully transferred and the mutated gene is successfully operating to produce the desired mutated protein and the desired enzymatic cleavage.

[8][9] Mayo does not dispute that the Mullan reference makes no mention of the formation of ATF-betaAPP in detectable amounts in brain homogenate. Mayo argues, and the district court found, that this claim limitation is "inherent" in Mullan because a successful transgenic procedure and ensuing enzymatic cleavage will produce ATF-betaAPP. However, this was not shown by Mullan, and there was no evidence that the formation and detection of ATF-betaAPP in the transgenic mouse brain with the Swedish mutation was known to persons of ordinary skill in the field of the invention. Inherency cannot be based on the knowledge of the inventor; facts asserted to be inherent in the prior art must be shown by evidence from the prior art. *Cf. In re Dembiczak,* 175 F.3d 994, 999, 50 USPQ2d 1614, 1617 (Fed.Cir.1999) (criticizing the "hindsight syndrome wherein that which only the inventor taught is used against its teacher"). The purpose of the rule of inherency is to accommodate common knowledge, knowledge that judges might not know but that would be known to practitioners in the field. *Finnigan Corp. v. Int'l Trade Comm'n,* 180 F.3d 1354, 1365, 51 USPQ2d 1001, 1009 (Fed.Cir.1999). On the law of anticipation, precedent has not improved on the words of Judge Learned Hand:

> No doctrine of the patent law is better established than that a prior patent or other publication to be an anticipation must bear within its four corners adequate directions for the practice of the patent invalidated. If the earlier disclosure offers no more than a starting point for further experiments, if its teaching will sometimes succeed and sometimes fail, if it does not inform the art without more how to practice the new invention, it has not correspondingly enriched the store of common knowledge, and it is not an anticipation.

Dewey & Almy Chemical Co. v. Mimex Co., 124 F.2d 986, 989 (2d Cir.1942).

We conclude that the legal requirements of anticipation were not met. The summary judgment of invalidity based on anticipation is reversed, and the case is remanded for further proceedings.

C

Mayo states that the Elan position on infringement is that the claims of the patents in suit cover all transgenic mice with the Swedish mutation, and that if the claims are construed as broadly as Elan proposes, they are invalid under § 103 or § 112. These issues were not decided by the district court; they are not before us for review.

D

We respond to the remarks of our colleague in dissent, for he has inaccurately perceived the "ground" on which our decision "rests." The ground of our decision is, simply, that a novel patented product is not "anticipated" if it did not previously exist.

The dissenter objects to what he calls the patenting of "existing inventions." We too object to the patenting of existing inventions. However, Elan is not patenting something that previously existed, for Elan's mouse did not exist. While Mullan surely had the concept of creating a transgenic ***1230** mouse with the mutated Swedish gene, as we have illustrated *ante,* Mullan did not make such a mouse and he did not tell (or know) which, if any, of the standard procedures from the scientific literature might be effective in achieving the complex series of transformations needed for a successful product. A general proposal to make a product that has not been made does not meet the criteria of "anticipation." Indeed, Mayo affirms in its brief that no mice had been made by Mullan; Mayo also affirms, contrary to the statements of the dissent, that "Mayo admits that some of the mice made according to the recipe [in the Mullan patent] will not have detectable ATF." Mayo brief at 19.

The dissent proposes that this decision will "have serious and unfortunate consequences in the future by permitting the securing of patent rights to existing inventions so long as the patent applicant identifies an inherent characteristic of that product that was not identified in the prior art," citing *In re Cruciferous Sprout Litigation,* 301 F.3d 1343 (Fed.Cir.2002). We repeat, the Mullan mouse did not exist, quite unlike the broccoli sprouts of the *Cruciferous Sprout Litigation,* "long well known in nature and eaten by humans for decades." *Id.* at 1346.

[10] The dissenter appears to urge the unpatentability of any product that has been suggested but never made. This approach would eliminate even the possibility of patent protection for any transgenic product that may have been envisioned but not yet produced. A better rule is the established law, whereby new products are not "anticipated" when they did not previously exist, whether or not the process for making them is generally known. Although our colleague postulates "serious and unfortunate consequences in the future" if the Elan mouse is deemed patentable, others may believe that without the possibility of a patent on a new transgenic mouse, the hypothetical mouse envisioned by Mullan might well remain no more than a hypothesis. Determination of which consequence is fortunate or unfortunate is an important policy question; the law of

anticipation as applied herein does not change existing policy.

[11] "Anticipation" in the patent sense means that the subject matter was previously known. A precatory suggestion of general procedures that may or may not succeed in producing the novel product, a product that has not previously been produced, does not convert the suggested product into a previously existing product. The witnesses were in agreement that at the time the Mullan application was filed neither Mullan nor anyone else (1) had made a mouse harboring the Swedish mutated gene, (2) knew whether the mouse DNA would accept the Swedish gene, (3) knew if the mouse cell would then express the human mutated protein of the Swedish family, or (4) knew whether the mouse enzymes would cleave the human mutated protein to produce human betaAP. Elan's expert Dr. Mobley stated, without disagreement, that "cells expressing the transgene have to correctly fold the protein, correctly modify it through glycosylation, correctly traffic it from internal to surface membranes, correctly traffic it through the endosomal pathway, and make it available to enzymes that modify it." Dr. Lieberburg, Elan's Chief Scientific and Medical Officer, stated that scientists were "at a great loss as to understand whether mice were even capable ... of ever generating specific APP fragments that could be studied for drug discovery."

It is undisputed that Mullan had not made a mouse by any of his proposed procedures, and all of the scientists agreed that it cannot be predicted which, if any, procedure will ultimately succeed. General ***1231** recipes of uncertain success do not convert a hoped-for product into one that previously existed. Our colleague in dissent states that despite Elan's statement that a successful mouse is a "tiny subset" of the transgenic mice that might be produced using Mullan's recipes, and despite the agreement of Mayo's witnesses with this scientific fact, the few successes that might be achieved (that is, that would possess the desired characteristics) form their own subset, thus placing the successful mouse in the prior art. That is not law of anticipation.

[12] We observe the dissent's statement that an inventor's own disclosure can be used against him to prove anticipation. That statement is inaccurate. Patentability requires novelty and unobviousness in light of the prior art, not in light of what the inventor knew and included in his patent application. "Anticipation is the epitome of obviousness," *Structural Rubber Products Co. v. Park Rubber Co.*, 749 F.2d 707, 716, 223 USPQ 1264, 1271 (Fed.Cir.1984), and both are measured by what was previously known to persons in the field of the invention, as discussed in precedent. And as we have stated, the scope of the Elan claims was not decided, nor was it decided whether the Elan claims, upon correct construction, would cover the specific Mayo mouse. These issues are not before us on this appeal.

Finally, we note the dissent's observation that Elan's claims do not "require ... a method of detection" of the ATF-beta APP. Elan has separate patents related to the method. *See, e.g.*, U.S. Patent No. 5,441,870 (Method for monitoring cellular processing of ?-amyloid precursor protein) to Seubert *et al.*, claiming: "A method for monitoring cellular processing of ?-amyloid precursor protein (?-APP) in cells, said method comprising detecting a soluble ?-APP fragment secreted from said cells, and a substance which specifically binds to said soluble ?-APP fragment, wherein the amino acid sequence of said ?-APP fragment extends substantially from the amino-terminus of ?-APP to the amino-terminus of ?-amyloid peptide (?-AP)."

REVERSED AND REMANDED.

DYK, Circuit Judge, dissenting.

The majority decision in this case rests upon the ground that an inventor's own disclosure may not be used under 35 U.S.C. § 102 as proof of anticipation by inherent disclosure in a prior art reference. This decision contradicts our own case law, which holds that knowledge of an inherent characteristic in the prior art is irrelevant. As we recently recognized in *In re Cruciferous Sprout Litigation*, 301 F.3d 1343, 1350 (Fed.Cir.2002), on the issue of inherency "[i]t matters not that those of ordinary skill heretofore may not have recognized these inherent characteristics." Here, as in *Cruciferous*, while Elan "may have recognized something quite interesting about those [mice], it simply has not invented anything new." *Id.* at 1351. This decision, if followed, will have serious and unfortunate consequences in the future by permitting the securing of patent rights to existing inventions so long as the patent applicant identifies an inherent characteristic of that product that was not identified in the prior art. That has never been our law. I respectfully dissent.

I

The patents asserted herein are U.S. Patent Nos. 5,612,486 ("the '486 patent") and 5,850,003 ("the '003 patent") (collectively "the Elan patents"). The sole independent claim of the '486 patent recites in relevant part:

> *A transgenic rodent* ... comprising a transgene encoding a heterologous APP ***1232** polypeptide having the Swedish mutation ... wherein the transgene is expressed to produce a human APP polypeptide having the Swedish mutation, and *wherein said polypeptide is processed to ATF-betaAPP in a sufficient amount to be detectable in a brain homogenate of said transgenic mouse.*

Claim 1 of the '486 patent (emphases added). The sole independent claim of the '003 patent recites in relevant part:

> *A transgenic rodent* ... comprising a transgene comprising ... a DNA segment encoding a heterologous APP polypeptide ..., wherein the transgene is expressed to produce a human APP polypeptide having the Swedish mutation, and *wherein said polypeptide is processed to ATF-betaAPP in a sufficient amount to be detectable in a brain homogenate of said transgenic rodent.*

Claim 1 of the '003 patent (emphases added). Because these claims are directed to transgenic rodents, the methods by which they are produced are not elements of the claims. Nor is there any claim to a method for detecting ATF- betaAPP.

Despite the clear language of the claims mandating their interpretation as *products* (transgenic rodents), much effort both at the district court and here on appeal has been expended on arguments incorrectly interpreting the claims in terms of methods. Elan argues, for example, that U.S. Patent No. 5,455,169 to Mullan (hereinafter "Mullan"), cited by the Mayo Foundation for Medical Education and Research (hereinafter "Mayo") as anticipating the claims of the Elan patents, fails to teach "*how to detect* ATF-betaAPP, much less *how to detect* the fragment in a brain homogenate." (Appellants' Br. at 23.) The claims of the Elan patents, however, require only *detectable* ATF-betaAPP and not a method of detection.

According to Elan, the '486 and '003 "patents required that its transgenic mice do all these things: [1] carry the APPSW transgene; [2] express the APPSW protein and [3] process the APPSW to ATF-betaAPP such that the levels of ATF-betaAPP are detectable." (Appellants' Br. at 21.) As admitted by Elan in its brief on appeal, "Elan does not dispute that the specification of the Mullan patent disclosed a transgenic mouse harboring a human APP gene with the Swedish mutation." *Id.* at 17. In other words, the first element was disclosed. On appeal Elan also does not contend that the second element was not disclosed. [FN1] Elan contests solely the third aspect of the claims. Elan bases the novelty of its claimed rodents on the "critical element-- processing APP to ATF-betaAPP in an amount sufficient to be detectable in a brain homogenate." *Id.* Mayo concedes that Mullan fails to expressly disclose this element of the claimed invention, but counters that this characteristic was inherent in the disclosure of Mullan. The only issue, therefore, is whether ***1233** the rodent of Mullan will inherently produce ATF-betaAPP in a sufficient amount to be detectable in its brain homogenate.

> FN1. The majority appears to suggest that this element was not disclosed in Mullan, but this issue was not raised on appeal. In any event, the Mullan patent discloses the second element, stating "[a]s a result of the transfer, the resultant transgenic non-human animal will express one or more variant APP codon 670/1 polypeptides." Mullan, col. 11, ll. 34-36. The majority cites no authority suggesting that any more detailed description was required. To be sure the Mullan reference must have been enabling in this respect, *In re Donohue,* 766 F.2d 531, 533, 226 USPQ 619, 621 (Fed.Cir.1985), and there may be a question as to whether it was enabling. But Elan has deliberately decided not to mount an enablement challenge to the Mullan patent, apparently for the reasons explained by the district court relating to potential for such arguments to invalidate Elan's own claims for lack of enablement. *Elan Pharms., Inc. v. Mayo Found. for Med. Educ. & Research,* 175 F.Supp.2d 1209, 1212 (N.D.Cal.2000).

II

On summary judgment the district court ruled that Mullan inherently anticipates the claims of the Elan patents, finding:

> The mice claimed in the patents-in-suit are merely a subset of the mice described in Mullan. Some of the mice made using the process disclosed in Mullan (which is essentially the same process disclosed in the patents-in-suit) would inevitably have detectable levels of ATF-betaAPP. Were Plaintiffs to contend otherwise, their own patents would not be enabled. Mullan therefore inherently includes the [detectable ATF-betaAPP] limitation of the final "wherein" clauses of the asserted claims.

Elan Pharms., Inc., 175 F.Supp.2d at 1212.

The majority disagrees, apparently because no extrinsic evidence of inherency existed in the prior art. The majority states:

> there was no evidence that the formation and detection of ATF-betaAPP in the transgenic mouse brain with the Swedish mutation was known to persons of ordinary skill in the field of the invention. Inherency cannot be based on the knowledge of the inventor; facts asserted to be inherent in the prior art must be shown by evidence from the prior art. *Cf. In re Dembiczak,* 175 F.3d 994, 999, 50 USPQ2d 1614, 1617 (Fed.Cir.1999) (criticizing the "hindsight syndrome wherein that which only the inventor taught is used against its teacher").

Ante at 1228.

But this is not the correct analysis. This is not an obviousness case. The injunction in *Dembiczak* against using an inventor's own disclosure against him was in the context of a section 103 obviousness determination requiring "the oft-difficult but critical step of casting the mind back to the time of invention, to consider the thinking

of one of ordinary skill in the art, guided only by the prior art references and the then-accepted wisdom in the field." 175 F.3d at 999, 50 USPQ2d at 1617 (citing *W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1553, 220 USPQ 303, 313 (Fed.Cir.1983), *cert. denied*, 469 U.S. 851, 105 S.Ct. 172, 83 L.Ed.2d 107 (1984)). The perceived problem with combining references using hindsight to render a claimed invention obvious is that it "simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability." *Id.* This fear of hindsight recreation in the context of obviousness determinations, however, is not applicable in the context of inherency.

There is simply no basis in our law to support the proposition that the source of proof for inherency must be found in the prior art and cannot be found in a patentee's own disclosure or other source. In *Continental Can Co. USA v. Monsanto Co.*, 948 F.2d 1264, 20 USPQ2d 1746 (Fed.Cir.1991), the court noted that "[t]o serve as an anticipation when the reference is silent about the asserted inherent characteristic, such gap in the reference may be filled with recourse to extrinsic evidence." *Id.* at 1268, 948 F.2d 1264, 20 USPQ2d at 1749. Thus evidence extrinsic to the cited prior art reference may be used, *i.e.*, the party raising the issue of inherency may fill in the gap in the disclosure using any source. The majority's contrary conclusion is incorrect as a matter of law, and directly contradicts our law, which has repeatedly recognized that the discovery of an inherent characteristic of an old product cannot be patented. *Cruciferous*, at 1350; ***1234***In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed.Cir.1990) ("When the claimed [inventions] are not novel they are not rendered patentable by recitation of properties, *whether or not these properties are shown or suggested in the prior art.*" (emphasis added)); *Titanium Metals Corp. of Am. v. Banner*, 778 F.2d 775, 782, 227 USPQ 773, 779 (Fed.Cir.1985) ("[I]t is immaterial, on the issue of their novelty, what inherent properties the [disclosed products] have or whether these applicants discovered certain inherent properties").

III

Because the disclosures of the Elan patents may be used as proof that the Mullan transgenic rodent inherently possessed the claimed characteristic, the remaining question is whether the Elan patents, in fact, provide that proof. They clearly do. The specification of the '003 patent teaches:

> Newly identified secreted fragments comprise amino-terminal portion of ?APP (A?) which remains after the cleavage and will be referred to hereinafter as the amino-terminal fragment form of ?APP (ATF-?APP) [ATF-betaAPP]. ATF-?APP is believed to be the product of an alternative secretory processing pathway for A?, which pathway is present even in normal (non-diseased) cells. It is further believed, however, that the alternate secretory pathway may be responsible for an essential event in the production of A? in diseased cells in patients, and that abnormal production of AFT-?APP may be involved in diseases related to A? plaque....
>
> Particularly preferred animal models for ?-secretase cleavage of A? are transgenic animals which express the Swedish mutation of the A? gene.... *It has been found that such transgenic animals, particularly transgenic mice, produce high quantities of the AFT[sic ATF]-?APP* which may [be] detected according to the methods of the present invention. *In particular, it has been found that Swedish mutation of A? produces quantities of the ATF-?APP which will usually be at least two-fold higher than wild type human ?APP expressed in animals.*

'003 patent, col. 12, ll. 21-42 (emphases added). The "discoveries" discussed in the preceding passage are two-fold: first, that the ?-secretase cleavage (metabolism) of the Swedish mutation form of APP to produce the ?-amyloid peptide (?A) results in a secondary "newly identified" fragment, ATF-? APP; and second, that the newly discovered fragment is found in "high quantities" in transgenic mice having the Swedish mutation form of APP.

As Elan concedes on appeal, "the specification of the Mullan patent disclosed a transgenic mouse harboring a human APP gene with the Swedish mutation." (Appellants' Br. at 17.) More than simply "harboring" the gene as suggested by Elan, however, Mullan discloses a transgenic mouse that will *express* the gene to produce the Swedish APP and then *metabolize* the APP to produce the ?-amyloid peptide for the study of the underlying biochemistry of that metabolism. Mullan, col. 11, ll. 5-36 ("[S]uch model systems provide a tool for defining the underlying biochemistry of APP and ?-amyloid metabolism.... The human variant APP codon ... can be transferred to a host non-human animal, such as a mouse. As a result of the transfer, the resultant transgenic non-human animal will express one or more variant APP codon 670/1 polypeptides."). As disclosed in the '003 specification, Swedish APP to ?-amyloid metabolism directly produces the "newly identified" ATF-?APP metabolite. '003 patent, col. 12, ll. 21-22. Further, transgenic mice that carry out the Swedish ***1235** APP to ?-amyloid metabolism produce "high quantities" of the ATF APP metabolite. *Id.* at col. 12, ll. 35-42. Because the claims are not limited to a particular "method of detection," but rather broadly recite the requirement that the fragments be "detectable," a mouse that metabolizes APP to produce the ?-amyloid peptide in sufficient amounts to permit the study of the underlying biochemistry of that metabolism would necessarily produce detectable amounts of the ATF-?APP metabolite.

Elan argues that "[t]he transgenic mice claimed by Elan's

patents are only a tiny, and at the time of Mullan unexpected, subset of the larger population of transgenic mice that might be produced by following the Mullan 'recipe.' " (Appellants' Reply Br. at 6.) In fact, the claimed mice are not a tiny subset of the mice disclosed in Mullan. To be sure, Mullan discloses a method for producing transgenic mice not all of which will successfully express the Swedish form APP. However, the Swedish form APP characteristic is disclosed in Mullan, and in each and every case of a mouse that processes Swedish form APP to produce the ?-amyloid chain as disclosed in the Mullan patent, that mouse will also produce ATF-?APP as claimed in the Elan patents. '003 patent, col. 12, ll. 21-42. Thus, the rule that "[i]nherency ... may not be established by probabilities or possibilities," *In re Oelrich*, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981) (citation omitted), is not violated by finding the claims of the Elan patent anticipated by a mouse according to Mullan (expressing and metabolizing the Swedish form APP), which will always possess the ATF-?APP characteristic.

The district court correctly concluded that the claims of the Elan patents are invalid as inherently anticipated by Mullan.

For the foregoing reasons, I respectfully dissent.

304 F.3d 1221, 64 U.S.P.Q.2d 1292

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United States Court of Customs and Patent Appeals.

Application of Herman HOEKSEMA.

Patent Appeal No. 7778.

Aug. 8, 1968.

Proceeding on appeal from a decision of the Patent Office Board of Appeals affirming examiner's rejection of remaining claim of application for a patent on a chemical compound, Serial No. 30,770. The United States Court of Customs and Patent Appeals, 379 F.2d 1007, affirmed. On rehearing, Smith, J., held that application on the chemical compound and a method for the making thereof was patentable over the prior art.

Reversed.

Kirkpatrick, J., dissented.

West Headnotes

[1] Patents ⇐16.25
291k16.25 Most Cited Cases

An invention as a whole, for patentability purposes, must be considered as the claimed compound and a way to produce it.

[2] Patents ⇐66(1.12)
291k66(1.12) Most Cited Cases

A compound would be considered patentable over the prior art even if the prior art disclosed the claimed compound, where the prior art did not disclose a way to produce it.

[3] Patents ⇐16.25
291k16.25 Most Cited Cases
(Formerly 291k18)

If the prior art of record fails to disclose or render obvious a method for making a claimed compound, at time invention was made, it may not be legally concluded that the compound itself is in possession of the public.

[4] Patents ⇐32
291k32 Most Cited Cases
Absence of a known or obvious process for making claimed compounds overcomes a presumption that the compounds are obvious, based on close relationships between their structures and those of prior art compounds.

[5] Patents ⇐66(1.12)
291k66(1.12) Most Cited Cases

Affidavit pointing out that reference relied on as precluding patentability did not disclose a process for producing different compounds claimed was sufficient to overcome cited reference as a patent-defeating reference.

[6] Patents ⇐66(1.12)
291k66(1.12) Most Cited Cases

Application on a chemical compound and a method for the making thereof was patentable over the prior art.

Patents ⇐328(2)
291k328(2) Most Cited Cases

3,094,460. Cited.
****270 *1494** Earl C. Spaeth, Kalamazoo, Mich., (Eugene O. Retter, George T. Johannesen, Kalamazoo, Mich., of counsel), for appellant.

Joseph Schimmel, Washington, D.C., (Jack E. Armore, Washington, D.C., of counsel), for Commissioner of Patents.

***1495** Before WORLEY, Chief Judge, and RICH, SMITH, ALMOND and KIRKPATRICK, [FNa1] Judges.

> FNa1. Senior District Judge, Eastern District of Pennsylvania, sitting by designation.

SMITH, Judge.

In our prior consideration of this appeal, we affirmed the decision of the Patent Office Board of Appeals, which had affirmed the examiner's rejection of the sole remaining claim of appellant's application, [FN1] In re Hoeksema, 379 F.2d 1007, 54 CCPA 1618 (1967). Bucause of the continuing importance of the questions involved, and the strong suggestion of error in our earlier opinion, we granted appellant's petition for a rehearing under the provisions of Rule 7 of this court, 55 CCPA , (October 5, 1967).

> FN1. Claim 1 in Serial No. 30770, filed May 23, 1960, for '9-D- Psicofuranosylpurine and 6-Substituted Derivatives.' Claims 2 and 11-25 stand allowed.

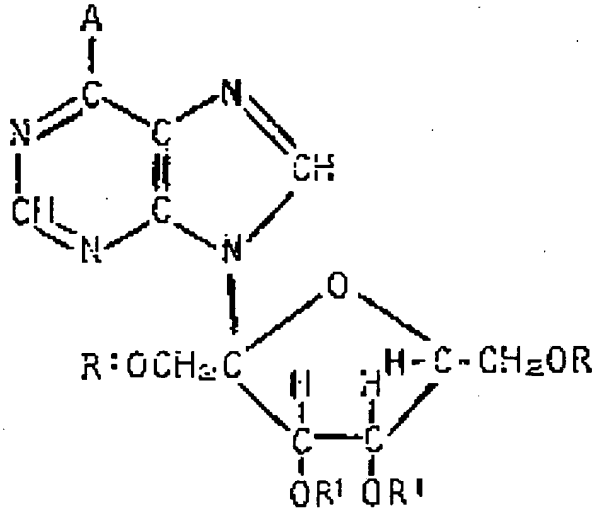
The parties filed new briefs, and the case was reargued on January 3, 1968. Upon reconsideration of our previous decision, we have concluded that our previous decision was erroneous and that a proper resolution of the issues requires that we reverse the decision of the board.

The facts are set forth in our original opinion. We shall assume familiarity with that statement of facts and shall here redevelop only those which we now believe were

previously misapprehended or misapplied and require the present decision.

The sole claim on appeal is directed to a chemical compound and reads as follows:

1. An N-psicofuranside having the formula:



wherein A is selected from the class consisting of hydrogen, the group-XR wherein R is selected from the class consisting of hydrogen, lower-alkyl, and lower-aralkyl, and X is selected from the class consisting of oxygen

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                                                R
sub2
and sulfur, and the group   --   N   <
                                                R
sub3
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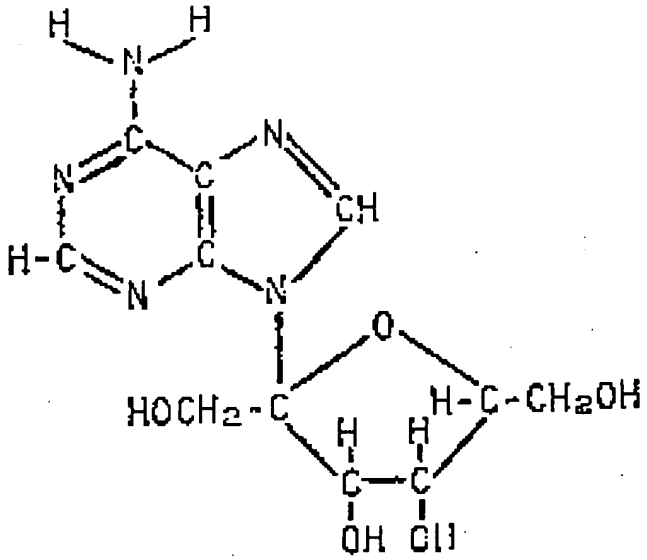
wherein R(2) is selected from the class consisting of hydrogen, lower-alkyl, lower-aralkyl, and lower-aryl, and R(3) is selected from the class consisting of lower-alkyl, lower-aralkyl, and lower-aryl, and R' is selected from ***1496** the class consisting of hydrogen, a hydrocarbon carboxylic acid acyl radical containing from two to twelve carbon atoms, inclusive, and a halo-, hydroxy-, lower-alkoxy-, amino-, cyano-, thiocyano-, and nitro-substituted hydrocarbon carboxylic acid acyl ****271** radical containing from two to twelve carbon atoms, inclusive.

That claim stands rejected under 35 U.S.C. § 103 as unpatentable over prior art, on this record limited solely to the De Boer et al. patent [FN2] (De Boer) which discloses a compound with the structural formula:

FN2. Patent No. 3,094,460, issued June 18, 1963 on an application filed January 20, 1959.



As we noted in our original opinion, the controversy here is limited to the substituent A at the 6-position of the purine ring system. Although a compound having De Boer's structure is not included in the appealed claim since A in the claim cannot be an unsubstituted or primary amino,

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--   N   <
                H ,
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the basic structure of the De Boer compound is similar to the structure of appellant's alkyl-amino and dialkylamino compounds. [FN3]

FN3. Appellant, in effect, admits that there is such a 'structural similarity' between his claimed compounds and the prior art compounds as to raise an 'inference of fact' that they are not patentable within the meaning of 35 U.S.C. § 103. See In re Papesch, 315 F.2d 381, 50 CCPA 1084 (1963); In re Mills, 281 F.2d 218, 47 CCPA 1185 (1960).

Despite this close structural similarity between the De Boer amino compound and the alkylamino and dialkylamino compounds included in the appealed claim, appellant chose not to submit a showing of unexpected properties in his claimed compounds. [FN4] Appellant asserted that his compounds were unobvious and patentable without such a showing. He urged that De Boer does not teach one of ordinary skill in the art how to make appellant's claimed compounds, and the examiner did not cite any other reference telling how they might be made. Therefore, in appellant's view, his claimed compounds are not ***1497** in

possession of the public, In re Brown, 329 F.2d 1006, 51 CCPA 1254 (1964). [FN5]

FN4. Such a showing often has been treated by this court as overcoming a case of 'prima facie obviousness' or the 'inference of fact' that the compounds are obvious. See, e.g., In re Papesch, supra note 3 and cases cited therein.

FN5. For the applicability of In re Brown, supra, to other factual contexts, see In re Bird, 344 F.2d 979, 982, 52 CCPA 1290, 1294 (1965); In re Sheppard, 339 F.2d 238, 242, 52 CCPA 859, 864 (1964); Dix-Seal Corp. v. New Haven Trap Rock Co., 236 F.Supp. 914, 921 (D.C.Conn. 1964).

In support of his position, appellant submitted an affidavit by Dr. Paul F. Wiley relating to the unavailability to the public of processes for preparing appellant's alkylamino and dialkylamino compounds. [FN6] Dr. Wiley's qualifications ****272** and competence as an expert to state facts and opinion in this area of chemistry were not challenged.

FN6. After setting forth his qualifications and stating that he had read and understood both appellant's application and the prior art patent, Dr. Wiley stated: THAT, 6-amino-9-D-psicofuranosylpurine is a systematic name for 'psicofuranine' which is disclosed in column 6, lines 46-62 of the aforesaid patent;
THAT, according to the aforesaid patent, 6-amino-9-D-psicofuranosylpurine is produced by a fermentation process involving the action of a specific microorganism, S. hygroscopicus var. decoyinine, in certain aqueous nutrient media;
THAT, there is no indication in the aforesaid patent (De Boer) that the aforesaid fermentation process could be used to produce 6-lower-alkylamio - 9 - D - psicofuranosylpurines, 6 - di - lower - alkylamino - 9 - D - psicofuranosylpurines, or other 6-substituted - amino - 9 - D - psicofuranosylpurines;
THAT, he does not believe the aforesaid fermentation process could be adapted to the production of the aforesaid 6-lower-alkylamino-9-D- psicofuranosylpurines, 6-di-lower-alkylamino-9-D-psicofuranosylpurines, or other 6-substituted - amino - 9 - D - psicofuranosylpurines;
THAT, the aforesaid 6-amino-9-psicofuranosylpurine could not be transformed by direct chemical substitution of the 6-amino group to a 6 - lower - alkylamino 9 - D -psicofuranosylpurine, a 6-di-lower alkylamino-9-D- psicofuranosylpurine, or other 6-substituted - amino - 9 - D - psicofuranosylpurines, and that such transformations could be carried out only by a complex multi-step procedure such as that described in the aforesaid patent application Serial No. 30,770. (Emphasis added.)

Regarding the Wiley affidavit, the examiner stated, in his Answer:

The affidavit * * * does not appear to be pertinent to the claim now on appeal because it is directed to the processes by which the De Boer et al. and appellant's compounds are prepared, and shows nothing unobvious for the instantly claimed compound.

Concerning the Wiley affidavit, the board cited a statement of this court in In re Riden, 318 F.2d 761, 50 CCPA 1411 (1963), to the effect that 'the method of making the compounds is a relevant fact to be considered in the question of obviousness of the compounds,' 318 F.2d at 764, 50 CCPA at 1415. But the board continued:

* * * This may be so but it is only one factor and, in our opinion, should never be the overriding one which appellant is here, in effect, urging.

Appellant states the first of two central questions to be decided in this rehearing as follows:

1) Appellant will admit his compounds are obvious and unpatentable if an obvious process is available to make them. Does it follow then that appellant's compounds are unobvious and patentable if an obvious process is not available to make them?

***1498** Within this context, appellant simplifies that question to: Is process obviousness relevant in deciding compound obviousness? [FN7]

FN7. To this extent, appellant has misstated his argument. That process obviousness is relevant in this context is clear from In re Riden, supra. See also In re Chapman, 357 F.2d 418, 53 CCPA 978 (1966); In re Burt, 356 F.2d 115, 53 CCPA 929 (1966); In re Schechter, 205 F.2d 185, 40 CCPA 1009 (1963).
We think appellant really means to say that the question is whether a claimed compound may be said to be legally obvious when no process for making that compound is shown in the prior art relied upon to establish legal obviousness under section 103.

The solicitor responds to the latter characterization of the question in the affirmative, pointing out that the first

question bears on the principle implicit in In re Brown, supra, that claimed compounds not distinguished in their properties over closely related prior art compounds are unpatentable thereover where the claimed compounds would be 'in possession of the public' in that a process for preparing them would be obvious to those of ordinary skill in the art.

In addition, the solicitor now refers to our prior opinion in which we noted that the facts in this case are closely analogous to those of In re Riden, supra, where we stated that the fact that the method of making the claimed compound is relevant, 379 F.2d at 1010, 54 CCPA at .

A recurring problem of analysis which confronted us as we prepared our previous opinion, and which still confronts us after the rehearing, has its genesis in a proper understanding of the issue as framed by appellant. In effect, appellant agrees that since the claimed product **273 is a homolog of a known compound, it would be prima facie 'obvious' under 35 U.S.C. § 103. But this agreement is conditioned on the proviso that there is in the prior art an 'obvious' process by which to make that compound.

In the context of section 103, we are not permitted to fragment a claimed invention in applying that section. The clear mandate of the statute which governs our analysis requires that we consider the invention as a whole in making the determination.

Thus, as we apply the statute to the present invention, we must ask first, what is the invention as a whole? Necessarily, by elementary patent law principles, it is the claimed compound, but, so considered, unless there is some known or obvious way to make the compound, the invention is nothing more than a mental concept expressed in chemical terms and formulae on a paper.

[1] We are certain, however, that the invention as a whole is the claimed compound and a way to produce it, wherefore appellant's argument has substance. There has been no showing by the Patent Office in this record that the claimed compound can exist because there is no showing of a known or obvious way to manufacture it; hence, it seems to *1499 us that the 'invention as a whole,' which section 103 demands that we consider, is not obvious from the prior art of record.

[2] While there are valid reasons based in public policy as to why this defect in the prior art precludes a finding of obviousness under section 103, In re Brown, supra, its immediate significance in the present inquiry is that it poses yet another difference between the claimed invention and the prior art which must be considered in the context of section 103. So considered, we think the differences between appellant's invention as a whole and the prior art are such that the claimed invention would not be obvious within the contemplation of 35 U.S.C. § 103.

While 35 U.S.C. § 102 is not directly involved in the issue on review, the conditions for patentability, novelty and loss of right to patent, there stated, may have relevance as to the disclosure which must be found in the prior art to find obviousness of an invention under section 103. In determining that quantum of prior art disclosure which is necessary to declare an applicant's invention 'not novel' or 'anticipated' within section 102, the stated test is whether a reference contains an 'enabling disclosure,' in the present context, a process by which the claimed compound could be made. In In re Le Grice, 301 F.2d 929, 49 CCPA 1124 (1962), we observed that the resolution of this issue required us to determine whether, as a matter of law, a reference without such a disclosure constituted a statutory time bar to an applicant's right to a patent. There, the issue was founded on 35 U.S.C. § 102(b), not § 103, but our conclusions have a certain pertinence here. We concluded, id. 301 F.2d at 936, 49 CCPA at 1134:

We think it is sound law, consistent with the public policy underlying our patent law, that before any publication can amount to a statutory bar to the grant of a patent, its disclosure must be such that a skilled artisan could take its teachings in combination with his own knowledge of the particular art and be in possession of the invention. * * *

In In re Brown, supra, this court discussed In re Von Bramer, 127 F.2d 149, 29 CCPA 1018 (1942), commenting that that opinion should not be construed to emcompass what had come to be called the 'Von Bramer doctrine.' There we stated, 329 F.2d at 1009, 51 CCPA at 1257:

* * * This doctrine, which appears to have resulted from In re Von Bramer et al., supra, seems over a period of years to have been tailored in some quarters to a principle which defeats the novelty of a chemical compound on the basis of a mere printed conception or a mere printed contemplation of a **274 chemical 'compound' irrespective of the fact that the so-called 'compound' described in the reference is not in existence or that there is no process shown in the reference for preparing the compound, or that there is no process *1500 known to a person having ordinary skill in the relevant art for preparing the compound. In other words a mere formula or a mere sequence of letters which constitute the designation of a 'compound,' is considered adequate to show that a compound in an application before the Patent Office, which compound is designated by the same formula or the same sequence of letters, is old. We do not think that the Von Bramer case should be so construed. (Emphasis added.)

To the extent that anyone may draw an inference from the Von Bramer case that the mere printed conception or the

mere printed contemplation which constitutes the designation of a 'compound' is sufficient to show that such a compound is old, regardless of whether the compound is involved in a 35 U.S.C. § 102 or 35 U.S.C. § 103 rejection, we totally disagree. * * *

We concluded, relying on In re Le Grice, supra, and E. I. DuPont de Nemours & Co. v. Ladd, 117 U.S.App.D.C. 246, 328 F.2d 547 (1964), that the 'true test of any prior art relied on to show or suggest that a chemical compound is old, is whether the prior art is such as to place the disclosed 'compound' in the possession of the public.' 329 F.2d at 1011, 51 CCPA at 1259.

While In re Le Grice was bottomed on an issue arising under 35 U.S.C. § 102 where the reference was a 'printed publication,' that test, in our view, is also properly applicable to issues arising under 35 U.S.C. § 103. See In re Brown, supra (pertinent portion quoted above); Deutsche Gold-Und Silber- Scheideanstalt v. Commissioner of Patents, 251 F.Supp. 624, 629-630 (D.D.C.1966), affirmed, 397 F.2d 656 (D.C.Cir. 1968).

[3][4] Thus, upon careful reconsideration it is our view that if the prior art of record fails to disclose or render obvious a method for making a claimed compound, at the time the invention was made, it may not be legally concluded that the compound itself is in the possession of the public. [FN8] In this context, we say that the absence of a known or obvious process for making the claimed compounds overcomes a presumption that the compounds are obvious, based on close relationships between their structures and those of prior art compounds.

> FN8. In Phillips Petroleum Co. v. Ladd, 219 F.Supp. 366 (D.D.C.1963), in considering a rejection arising under 35 U.S.C. § 102, the District Court agreed with this court that the mere naked statement of the invention does not put anyone in possession of the invention. That court was careful to note that no process had been shown in the reference for preparing the compound and that no process was known to one of ordinary skill in the art for preparing the compound.
> In Ex parte Wall, 156 USPQ 95 (P.O.Bd.App.1964), the board, considered a rejection under 35 U.S.C. § 102 of a claim reading 'Perfluorostyrene.' In reversing the examiner, the board commented that the examiner did not contend that the reference disclosed how perfluorostyrene is made, nor did he point to any extraneous evidence which would indicate that those skilled in the art knew how to make that compound.

The second aspect of the questions presented by this rehearing involves ***1501** the issue of whether the burden is on the Patent Office to provide the evidence on which to predicate process obviousness.

35 U.S.C. § 101 states, in its preamble, that an applicant is entitled to a patent unless certain patent-defeating provisions are met. The substantive patent-defeating provisions are encompassed in 35 U.S.C. §§ 100-103.

As we have stated, the Patent Office search resulted in citation of the De Boer reference which, under the prevailing law, rendered appellant's claimed compounds prima facie obvious. In other ****275** words, its citation shifted to appellant the burden of going forward with contrary evidence. Appellant filed the affidavit of Dr. Wiley which points out as a fact that De Boer-- the only reference being relied on-- does not disclose a process for producing the different compounds here claimed.

[5] We think that portion of the Wiley affidavit set forth, supra note 6, states facts which were legally sufficient to overcome the position of the Patent Office as to the legal effect under section 103 of the De Boer reference. [FN9] Appellant's responsibility to overcome this reference as a 'patent-defeating' reference under section 103 at that point in the prosecution was only to overcome De Boer as a reference pertinent to the issue of obviousness under section 103.

> FN9. We think this approach to be eminently fair to all parties and in accord with the opinion of the Supreme Court in Graham, in its requiring that all of the pertinent evidence be considered while yet leaving the primary responsibility for sifting out unpatentable material with the Patent Office, Graham v. John Deere Co., 383 U.S. 1 at 18, 86 S.Ct. 684, 15 L.Ed.2d 545.
> It would be practically impossible for an applicant to show that all known processes are incapable of producing the claimed compound.

We think the Wiley affidavit is clearly sufficient for this purpose. The affidavit points out that there is no indication in the De Boer patent that the fermentation process used to produce De Boer's compounds could be used to produce appellant's compounds. Since we are of the view that the method for making the compounds is an integral part of the 'invention as a whole' which we must consider under section 103, we conclude that the burden of going forward with proofs to support its position as to obviousness of the claimed invention shifted to the Patent Office upon appellant's filing of the Wiley affidavit.

[6] The failure of the Patent Office to produce such evidence requires that the decision of the board be reversed.

***1494** Reversed.

***1501** WORLEY, C.J., did not participate.

KIRKPATRICK, Judge (dissenting).

I am unable to agree with the result reached by the majority. The reasons for my dissent appear in the overrruled opinion In re Hoeksema, 379 F.2d 1007, 54 CCPA 1618 (1967).

399 F.2d 269, 55 C.C.P.A. 1493, 158 U.S.P.Q. 596

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United States Court of Appeals for the Federal Circuit

99-1416, -1433

PURDUE PHARMA L.P. and THE PURDUE FREDERICK COMPANY,

Plaintiffs-Appellants,

v.

FAULDING INC., FAULDING PHARMACEUTICAL CO.,

FAULDING SERVICES, INC., and PUREPAC PHARMACEUTICAL CO.,

Defendants-Cross Appellants,

and

ZENECA INC.,

Defendant.

S. Leslie Misrock and Victor N. Balancia, Pennie & Edmonds LLP, of New York, New York, argued for plaintiffs-appellants. With them on the brief was Todd A. Wagner, and Stanton T. Lawrence, III, Pennie & Edmonds LLP, of Washington, DC.

Steven J. Lee, Kenyon & Kenyon, of New York, New York, argued for defendants-cross appellants. With him on the brief were Paul H. Heller, Edward J. Handler, III, Charles A. Weiss, William G. James, II, and Mark I. Koffsky. Of counsel on the brief was E. Brendan Magrab, Faulding, Inc., of Elizabeth, New Jersey. Of counsel were Jack B. Blumenfeld, and Karen Jacobs Louden, Morris, Nichols, Arsht & Tunnell, of Wilmington, Delaware.

Appealed from: United States District Court for the District of Delaware

Chief Judge Joseph J. Farnan, Jr.

United States Court of Appeals for the Federal Circuit

99-1416,-1433

PURDUE PHARMA L.P. and THE PURDUE FREDERICK COMPANY,

Plaintiffs-Appellants,

v.

FAULDING INC., FAULDING PHARMACEUTICAL CO.,

FAULDING SERVICES, INC., and PUREPAC PHARMACEUTICAL CO.,

Defendants-Cross-Appellants,

and

ZENECA INC.,

Defendant.

DECIDED: October 25, 2000

Before PLAGER, Circuit Judge, SMITH, Senior Circuit Judge, and BRYSON, Circuit Judge.

BRYSON, Circuit Judge.

Purdue Pharma L.P. and The Purdue Frederick Company (collectively Purdue) own U.S. Patent No. 5,672,360 (the '360 patent), which is drawn to methods of treating pain in patients by administering an opioid, such as morphine, once a day. Purdue brought a patent infringement suit against Faulding Inc., Faulding Pharmaceutical Co., Faulding Services, Inc., and Purepac Pharmaceutical Co. (collectively Faulding) in the United States District Court for the District of Delaware. After a bench trial, the district court found that Faulding had infringed the asserted claims of the '360 patent but that the claims were invalid. Purdue appeals from the finding of invalidity, and Faulding cross-appeals from the finding of infringement. We uphold the court's ruling invalidating the asserted claims of the '360 patent; we do not reach Faulding's cross-appeal on the issue of infringement.

I

In 1984 Purdue introduced a sustained-release, twice-a-day oral morphine formulation. Sustained-release formulations represent a significant advance over immediate-release morphine formulations because immediate-release formulations need to be administered every four hours, a schedule that interferes with the patient's sleep and subjects the patient to cycles of pain that are difficult to control.

After its success with its twice-a-day formulation, Purdue sought to develop a sustained-release oral morphine formulation that would need to be administered only once a day. The work of its researchers initially led to the issuance of U.S. Patent No. 5,478,577 (the '577 patent), which discloses a once-a-day formulation exhibiting a rapid initial rise in the opioid concentration in the patient's blood.

During the same period, Faulding was developing long-lasting opioid anti-pain formulations as well. In 1996, Faulding began marketing its oral sustained-release morphine formulation in the United States under the trade name Kadian. The package insert accompanying Kadian states that it may be administered either once or twice a day.

Shortly after Faulding began selling Kadian in this country, Purdue brought suit against Faulding and Zeneca Inc., alleging that the manufacture, sale, and use of Kadian as a once-a-day morphine formulation infringed the '577 patent. At the time the suit was filed, the inventors of the '577 patent had pending before the Patent and Trademark Office U.S. Patent Application Serial No. 08/578,688 (the '688 application), which claimed priority to the application that led to the '577 patent.

While the litigation over the '577 patent was pending, Purdue's counsel canceled the pending claims of the '688 application and amended the application to add all new claims. The application was allowed as amended, and it issued as the '360 patent on September 30, 1997. No art rejections were made against the issued claims. The only prosecution history is contained in a handwritten interview summary in which the examiner stated that the "new claims are supported by the specs."

Purdue asserts that the once-a-day formulation described in the treatment method of the '360 patent, which results in a substantial fluctuation in the opioid concentration in the patient's blood between the maximum concentration level and the concentration level at the end of the 24-hour dosage period, was contrary to the prevailing view at the time that sustained-release formulations should produce minimal fluctuations in the opioid concentration level during the dosing interval. That aspect of the invention is reflected in each of the claims of the '360 patent, including claims 2, 4, and 11, the three asserted claims at issue in this case. Claims 1 and 9, on which the three asserted claims depend, both contain a limitation requiring that the maximum plasma concentration of the opioid be more than twice the plasma level of the opioid 24 hours after administration of the drug. The pertinent claims of the '360 patent at issue in this case read as follows:

1. A method of effectively treating pain in humans, comprising orally administering to a human patient on a once-a-day basis an oral sustained release dosage form containing an opioid analgesic or salt thereof which upon administration provides a time to maximum plasma concentration (T_{max}) of said opioid in about 2 to about 10 hours and a maximum plasma concentration (C_{max}) which is more than twice the plasma level of said opioid at about 24 hours after administration of the dosage form, and which dosage form provides effective treatment of pain for about 24 hours or more after administration to the patient.

2. The method of claim 1, wherein the T_{max} occurs in about 2 to about 8 hours after oral administration of said dosage form.

4. The method of claim 1, wherein said opioid analgesic is morphine sulfate.

> I. A method of effectively treating pain in humans, comprising orally administering to a human patient on a once-a-day basis an oral sustained release dosage form containing an opioid analgesic or salt thereof which at steady-state provides a time to maximum plasma concentration (T_{max}) of said opioid in about 2 to about 10 hours and a maximum plasma concentration (C_{max}) which is more than twice the plasma level of said opioid at about 24 hours after administration of the dosage form, and which dosage form provides effective treatment of pain for about 24 hours or more after administration to the patient.

11. The method of claim 9, wherein said opioid analgesic is morphine sulfate.

Shortly after the '360 patent issued, Purdue amended the complaint in the pending litigation against Faulding and Zeneca by dropping its claims under the '577 patent and asserting infringement of the '360 patent. Faulding and Zeneca asserted various counterclaims, including non-infringement and invalidity, and a bench trial was held on liability. During trial, the district court dismissed the claims against Zeneca. Following the trial, the court held that Faulding's production and sale of Kadian infringed the asserted claims of the '360 patent, but that the claims were invalid because they lacked the written description required by 35 U.S.C. § 112, first paragraph. The court then entered final judgment on the tried issues under Fed. R. Civ. P. 54(b).

II

The validity issue in this case is whether the limitation "a maximum plasma concentration (C_{max}) which is more than twice the plasma level of said opioid at about 24 hours after administration of the dosage form [C_{24}]" was adequately described in the disclosure of the '688 application as originally filed. The trial court found that it was not.

In order to satisfy the written description requirement, the disclosure as originally filed does not have to provide in haec verba support for the claimed subject matter at issue. See Fujikawa v. Wattanasin, 93 F.3d 1559, 1570, 39 USPQ2d 1895, 1904 (Fed. Cir. 1996). Nonetheless, the disclosure "must . . . convey with reasonable clarity to those skilled in the art that . . . [the inventor] was in possession of the invention." Vas-Cath Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). Put another way, one skilled in the art, reading the original disclosure, must "immediately discern the limitation at issue" in the claims. Waldemar Link GmbH & Co. v. Osteonics Corp., 32 F.3d 556, 558, 31 UPSQ2d 1855, 1857 (Fed. Cir. 1994). That inquiry is a factual one and must be assessed on a case-by-case basis. See Vas-Cath, 935 F.2d at 1561, 19 USPQ2d at 1116 ("Precisely how close the original description must come to comply with the description requirement of § 112 must be determined on a case-by-case basis."). When the question whether a patent satisfies the written description requirement is resolved by a district court sitting as the trier of fact, we review the court's decision for clear error. See Tronzo v. Biomet, Inc., 156 F.3d 1154, 1158, 47 USPQ2d 1829, 1832 (Fed. Cir. 1998); Gentry Gallery, Inc. v. Berkline Corp., 134 F.3d 1473, 1479, 45 USPQ2d 1498, 1502 (Fed. Cir. 1998).

Purdue contends that the district court made various legal errors in its analysis of the written description issue and that its factual finding on that issue was clearly erroneous. Turning first to the district court's factual analysis, we conclude that the court's finding on the written description issue did not constitute clear error.

A

The district court found that the specification of the '360 patent fails to convey that the C_{max}/C_{24} limitation was encompassed within Purdue's original invention. Purdue attacks that finding on several fronts, but its arguments are unpersuasive.

1

Purdue first argues that the C_{max}/C_{24} limitation is supported by the portion of the specification that describes the invention as not having a "generally flat" or "substantially flat" morphine plasma concentration curve. The passage of the specification on which Purdue relies reads as follows:

> The state-of-the-art approach to controlled release opioid therapy is to provide formulations which exhibit zero order pharmacokinetics and have minimal peak to trough fluctuation in opioid levels with repeated dosing. This zero order release provides very slow opioid absorption, and a generally flat serum concentration curve over time. A flat serum concentration curve is generally considered to be advantageous because it would in effect mimic a steady-state level where efficacy is provided but side effects common to opioid analgesics are minimized. . . .
>
> It has now been surprisingly discovered that quicker and greater analgesic efficacy is achieved by 24 hour oral opioid formulations which do not exhibit a substantially flat serum Concentration curve, but which instead provide a more rapid initial opioid release so that the minimum effective analgesic concentration can be more quickly approached in many patients who have measurable if not significant pain at the time of dosing. . . . Also surprising and unexpected is the fact that while the methods of the present invention achieve quicker and greater analgesic efficacy, there is not a significantly greater incidence in side effects which would normally be expected as higher peak plasma concentrations occur.

'360 patent, col. 5, ll. 24-55. The district court disagreed with Purdue's argument that the phrase "formulations which do not exhibit a substantially flat serum Concentration curve" refers to the C_{max}/C_{24} ratio of more than two that was added in the amended claims. Instead, the court concluded that the term refers to the feature of rapid opioid release that was recited in the original claims of the application and was described in the specification as "critical" to the invention. The court's finding is supported by the context in which the statement appears, and it is consistent with the claims as originally filed, which defined the formulation as providing "an initially rapid rise . . . by providing an absorption half-life [i.e., the time required for one-half of the absorbable opioid to be absorbed into the plasma] from about 1 to 8 hours."

In addition to finding that the "substantially flat" language in the specification did not refer to the C_{max}/C_{24} limitation, the trial court found that even if that language were understood to relate to the fluctuation in opioid concentration in the blood between the maximum concentration level and the concentration level after 24 hours, one skilled in the art would not understand the term "substantially flat" to mean a fluctuation of 100% or less.

At trial, Purdue offered expert testimony that the term "flat" is understood in the field to mean a fluctuation of 100% or less in the concentration of opioid between the maximum level and the level after 24 hours, i.e., a C_{max}/C_{24} ratio of two or less. The court, however, was unpersuaded. As the court explained, one of Purdue's experts, Dr. Goldenheim, described another sustained-release morphine formulation, Roxanol SR, as having a "flat" serum concentration curve, even though he acknowledged that it has a fluctuation of over 100%. In addition, the court found that the publications relied upon by Purdue did not substantiate Purdue's assertion that "flat" means fluctuations of 100% or less. Moreover, the court stated that even if it accepted Purdue's argument that "flat" means a fluctuation of 100% or less, "the use of the modifier 'substantially' in the specification, indicates that the word 'flat' as used in the '360 patent specification, does not even refer to the precise quantification urged by Purdue."

One of the publications Purdue relied on at trial was International Publication Number WO 94/22431, on which Kabi Pharmacia AB was the applicant. The Kabi application provides pharmacokinetic profiles for two different morphine formulations, CR-A and CR-B. The trial court found that for the CR-A formulation the C_{max} level was more than twice as great as the C_{24} level, and that for the CR-B formulation the C_{max} level was less than twice as great as the C_{24} level. Nonetheless, the Kabi application described both formulations as having "low" fluctuations. The court therefore found that the Kabi application "fails to support Purdue's contention that one skilled in the art understands 'flat' to mean fluctuations of less than 100%."

Purdue argues that Kabi's CR-A is a twice-a-day formulation and that the court's reliance on that formulation was therefore misplaced. As noted by Faulding, however, the data in the Kabi application was based on the administration of a single dose of morphine. For that reason, the court was not mistaken in relying on the description of the C_{max}/C_{24} ratio for the CR-A formulation in concluding that the Kabi application fails to support Purdue's argument that one skilled in the art would interpret "substantially flat" to mean a C_{max}/C_{24} ratio of two or less.

Purdue also argues that the trial court was confused with respect to Dr. Goldenheim's testimony regarding Roxanol SR, which Dr. Goldenheim characterized as having a flat profile. Purdue argues that Roxanol SR is approved only as an eight-hour formulation and that the C_{max}/C_8 ratio of Roxanol SR is less than 2. On cross-examination, however, Dr. Goldenheim was asked to calculate a C_{max}/C_{12} ratio for Roxanol SR from an article containing pharmacokinetic studies of the drug. From the data presented in the paper, Dr. Goldenheim determined that the C_{max}/C_{12} ratio for Roxanol SR is greater than two, and he characterized that C_{max}/C_{12} ratio as "pretty flat."

That evidence is meaningless, Purdue asserts, because Roxanol is not described as being approved for twice-a-day administration. Dr. Goldenheim's testimony on cross-examination, however, related to the morphine concentration in the Roxanol SR formulation after 12 hours, and the district court reasonably interpreted Dr. Goldenheim's testimony as a concession that a C_{max}/C_{12} ratio greater than two would still be considered "flat." From that evidence, the district court permissibly concluded that a person skilled in the art would not necessarily interpret the term "flat" to be limited to a concentration level ratio less than or equal to two.

Finally, Purdue asserts that the trial court erroneously failed to consider the teachings of the Morella patents. Those patents, Purdue contends, establish that by 1993 it was understood in the field that a flat pharmacokinetic profile constituted a profile having fluctuations of 100% or less. For example, Purdue argues, U.S. Patent No. 5,202,128, to Morella et al. states that an advantage of the morphine formulations of the invention is that the peak-to-trough variation will be between 60% and 100%, which has been described as a "flat plasma morphine concentration time profile." Purdue, however, does not point to anything in the Morella patents that suggests that if the peak-to-trough variation is greater than 100%, the concentration profile would not be considered flat. The Morella patents therefore do not in any way undermine the district court's finding that a person of ordinary skill in the art would not understand the term "substantially flat" to denote a C_{max}/C_{24} ratio of two or less.

Purdue argues that even if the passage from the specification referring to the "substantially flat serum Concentration curve" does not provide the required written description for the C_{max}/C_{24} ratio recited in the claims, the examples set forth in the patent provide adequate support for that limitation. Purdue relies on Example 1 (fed and fasted) and Example 3 (fed only) to support the claimed limitation, as the morphine formulation in both examples resulted in a C_{max}/C_{24} ratio greater than two.

The district court rejected Purdue's argument, pointing out that the specification also contains examples in which the C_{max}/C_{24} ratio is less

than two and that nothing in the specification indicates to the skilled artisan which examples embody the claimed invention and which do not. We conclude that the district court did not commit clear error in finding that the examples do not provide sufficient support for the C_{max}/C_{24} limitation.

The specification sets forth seven examples. Values for C_{max} and C_{24} are provided for only the first three. Other pharmacokinetic data are provided as well, and morphine concentrations are provided for times other than 24 hours after administration of the drug. Although the examples provide the data from which one can piece together the C_{max}/C_{24} limitation, neither the text accompanying the examples, nor the data, nor anything else in the specification in any way emphasizes the C_{max}/C_{24} ratio. The district court therefore reasonably concluded that one of ordinary skill in the art would not be directed to the C_{max}/C_{24} ratio as an aspect of the invention.

The case of In re Ruschig, 379 F.2d 990, 154 USPQ 118 (CCPA 1967), is instructive here. In that case our predecessor court affirmed the holding of the Patent Office Board of Appeals that one of the claims, adopted for purposes of interference, was not supported by the disclosure. The claim at issue in that case was directed to a single compound. The applicants argued that, although the compound itself was not disclosed, one skilled in the art would find support for the claimed compound in the general disclosure of the genus of compounds to which the claimed compound belonged. The Ruschig court rejected that argument, stating that

> [i]t is an old custom in the woods to mark trails by making blaze marks on the trees. It is of no help in finding a trail or in finding one's way through the woods where the trails have disappeared—or have not yet been made, which is more like the case here—to be confronted simply by a large number of unmarked trees. We are looking for blaze marks which single out particular trees. We see none.

Id. at 994-95, 154 USPQ at 122. Although this case differs from Ruschig in that what was disclosed in Ruschig was a genus encompassing potentially half a million compounds, the rationale applies equally to this case, in which the disclosure of the '360 patent discloses a multitude of pharmacokinetic parameters, with no "blaze marks" directing the skilled artisan to the C_{max}/C_{24} ratio or what value that ratio should exceed. See id. at 994, 154 USPQ at 122 ("Specific claims to single compounds require reasonably specific supporting disclosure and while we agree with the appellants, as the board did, that naming is not essential, something more than the disclosure of a class of 1000, or 100, or even 48, compounds is required."). As Ruschig makes clear, one cannot disclose a forest in the original application, and then later pick a tree out of the forest and say "here is my invention." In order to satisfy the written description requirement, the blaze marks directing the skilled artisan to that tree must be in the originally filed disclosure. See id. at 994-95, 154 USPQ at 122; Fujikawa, 93 F.3d at 1570-71, 39 USPQ2d at 1905; Martin v. Mayer, 823 F.2d 500, 505, 3 USPQ2d 1333, 1337 (Fed. Cir. 1987) ("It is 'not a question of whether one skilled in the art might be able to construct the patentee's device from the teachings of the disclosure. . . . Rather, it is a question whether the application necessarily discloses that particular device.'") (quoting Jepson v. Coleman, 314 F.2d 533, 536, 136 USPQ 647, 649-50 (CCPA 1963)). Under that standard, we conclude that the district court did not commit clear error in finding that nothing in the '688 application "'necessarily' . . . described the later claimed subject matter" of the '360 patent. In re Daniels, 144 F.3d 1452, 1456, 46 USPQ2d 1788, 1790 (Fed. Cir. 1998).

In the case of the '360 patent, there is nothing in the written description of Examples 1 and 3 that would suggest to one skilled in the art that the C_{max}/C_{24} ratio is an important defining quality of the formulation, nor does the disclosure even motivate one to calculate the ratio. For example, the description of Example 1 states that

> [p]lasma morphine concentrations were used for calculation of phamacokinetic parameters including: (a) absorption and elimination rates; (b) area under the curve (AUC); (c) maximum plasma concentration (C_{max}); (d) time to maximum plasma concentration [(]T_{max}); (e) $T_{1/2}$ (elimination).

'360 patent, col. 16, ll. 24-29. Figure 9 of the patent graphically represents the mean morphine plasma concentration-time profile for Examples 1 and 2, as well as for the control formulation, MS-Contin. In discussing Figure 9, the disclosure merely states that "it can be seen that the formulation of Example 1 attains a higher and earlier C_{max} but a slightly lower extent of morphine absorption than the formulation of Example 2." Id. at col. 21, ll. 8-11.

These statements and the calculation of the listed pharmacokinetic parameters are consistent with how the inventors characterize the invention, as the specification states earlier that "inventive sustained release once-a-day formulations may be characterized by the fact that they are designed to provide an initially rapid rate of rise in the plasma concentration of said opioid characterized by providing an absorption half-life from about 1 to about 8 hours," '360 patent, col. 6, ll. 1-5, and also that "the inventive formulations may be further characterized by having a surprisingly fast time to peak drug concentration (i.e., t_{max})," id. at col. 6, ll. 10-12. As can be seen from these excerpts from the specification, however, there is nothing in the written disclosure as originally filed directing the skilled artisan to the C_{max}/C_{24} ratio.

What the '360 patentees have done is to pick a characteristic possessed by two of their formulations, a characteristic that is not discussed even in passing in the disclosure, and then make it the basis of claims that cover not just those two formulations, but any formulation that has that characteristic. This is exactly the type of overreaching the written description requirement was designed to guard against. See Vas-Cath, 935 F.2d at 1561, 19 USPQ2d at 1115 ("Adequate description of the invention guards against the inventor's overreaching by insisting that he recount his invention in such detail that his future claims can be determined to be encompassed within his original creation.") (quoting Rengo Co. v. Molins Mach. Co., 657 F.2d 535, 551, 211 USPQ 303, 321 (3d Cir. 1981)).

Purdue characterizes this case as one in which, at bottom, the applicants claimed less than they disclosed. Using the data from Examples 1 and 3, the skilled artisan can establish a range for the C_{max}/C_{24} ratio of 1.28 to 3.43. Thus, according to Purdue, the claim limitation requiring C_{max}/C_{24} to be greater than two is narrower than the range disclosed in the specification. Purdue asserts that it did not consider claims in which the C_{max}/C_{24} ratio was less than two to be patentable in light of the prior art, and that its willingness to settle for claims narrower than the invention it disclosed does not create a written description problem.

Because the specification does not clearly disclose to the skilled artisan that the inventors of the '360 patent considered the C_{max}/C_{24} ratio to be part of their invention, it is immaterial what range for the C_{max}/C_{24} ratio can be gleaned from the examples when read in light of the claims. There is therefore no force to Purdue's argument that the written description requirement was satisfied because the disclosure revealed a broad invention from which the claims carved out a patentable portion.

B

Apart from the asserted factual flaws in the district court's analysis, Purdue contends that the trial court committed several errors of law that affected the court's analysis of the written description issue and require reversal. We have examined each of the claimed legal errors and conclude that the district court did not commit any error of law that had a material effect on the court's judgment.

1

First, Purdue argues that the district court applied the wrong legal test for determining whether the written description requirement was satisfied. Purdue acknowledges that the district court recited the correct test, as set forth in this court's decision in the Vas-Cath case, supra, but argues that the court actually applied a different test—one that was specifically rejected in Vas-Cath. In particular, Purdue relies on a statement in the district court's opinion in which the court commented that "viewing the examples collectively, as the Court believes must be done because there is no way to determine which embody the invention and which do not, the examples illustrate a range between 1.48 and 3.43." That comment, according to Purdue, shows that the district court required the specification to set forth what the invention is and what it is not, which is not the correct test under the written description requirement.

Purdue has misinterpreted the quoted passage from the district court's opinion. The court did not insist that the examples identify exactly what constitutes the claimed invention and what does not; instead, the court simply noted that it had to view all of the examples collectively because the specification did not state that any particular examples pertained to the invention that was recited in the amended claims. Under the circumstances, it was entirely appropriate for the district court to view all of the examples together in its effort to determine whether the disclosure as filed contained a sufficient written description of the invention; indeed, that approach was necessary in order for the court to determine that the inventor "had possession at that time of the later claimed subject matter." Vas-Cath, 935 F.2d at 1563, 19 USPQ2d at 1116.

Purdue makes the related contention that the district court did not view the disclosure as a whole in determining whether the written description requirement was satisfied. Again, we read the district court's opinion differently. Although the district court discussed the examples and the text of the specification separately, it is clear from the court's opinion that it concluded that the specification as a whole did not support the asserted claims of the '360 patent; there is nothing in the court's opinion suggesting that the court considered that any one segment of the specification, standing alone, had to provide the full support for the amended claims.

2

Purdue next argues that the district court committed legal error by looking to the written description portion of the patent, rather than the claims, to define the invention for purposes of the written description analysis. The district court made no error in this regard. The court noted that it "must necessarily look to the claim language to determine if the specification supports what is now claimed," and it further explained that it could not consider the amended claims themselves, which did not appear in the application as filed, "to show that at the time of filing the inventor was in possession of what is now claimed." We interpret those remarks as simply articulating the correct legal principles that the amended claims define the invention, that the support for the invention must be found in the specification as filed, and that the amended claims could not be used to provide that support.

3

Finally, Purdue contends that the district court improperly disregarded the findings of the examiner, who stated in an interview summary at the time the amended claims were added to the application that the new claims "are supported by the specs." Purdue argues that the district court should have deferred to the examiner's finding on that issue and that the district court failed to do so because the court improperly regarded the written description issue to be an issue of law rather than an issue of fact.

It is true that the district court at one point in its opinion characterized validity as an issue of law. Notwithstanding that isolated statement, the court's lengthy and thorough opinion makes it abundantly clear that the court understood that the question whether the written description requirement was satisfied is a question of fact. Moreover, the district court expressly addressed the examiner's statement on which Purdue relies and found it insufficient on the merits to carry the day for Purdue. The court explained that it did not regard the examiner's cryptic statement as directly applicable to the written description requirement but added that even if the examiner's statement was directed to the written description requirement, "any deference due to the Patent Examiner has been overcome by Faulding's clear and convincing evidence that the specification does not support the asserted claims of the '360 Patent." Thus, the court rejected the

examiner's statement on which Purdue relies not because of a misconception about the nature of the issue before it, but because the court did not find the examiner's statement persuasive in light of all the evidence in the case.

Relying on the Supreme Court's decision in Dickinson v. Zurko, 527 U.S. 150, 50 USPQ2d 1930 (1999), Purdue makes the related argument that the district court should have sustained the examiner's decision on the written description issue as long as it was supported by substantial evidence. The short answer to that argument is that this was an infringement action that originated in the district court, not an appeal from a decision of the Patent and Trademark Office Board of Appeals and Interferences, which was at issue in Zurko. The Administrative Procedure Act standard of review adopted in Zurko therefore has no application here. To be sure, as we have noted, the decision of the Patent and Trademark Office with respect to patentability is accorded deference in district court litigation, deference that takes the form of the presumption of validity that is accorded to issued patents under 35 U.S.C. § 282. See Fromson v. Advance Offset Plate, Inc., 755 F.2d 1549, 1555, 225 USPQ 26, 31 (Fed. Cir. 1985). The court, however, was not bound by the examiner's finding in the ex parte application proceeding that the new claims were supported by the specification, particularly in light of the fact that the court heard extensive evidence on the issue in an adversary hearing, none of which was before the patent examiner.

III

Because we have upheld the district court's determination that the asserted claims of the '360 patent are invalid, it is unnecessary to address Faulding's cross-appeal from the district court's finding of infringement.

AFFIRMED.

C

United States Court of Customs and Patent Appeals.

Application of Lynn B. WAKEFIELD and Frederick C. Foster.

Patent Appeal No. 8192.

March 12, 1970, As Modified on Denial of Rehearing May 21, 1970.

The Patent Office Board of Appeals affirmed rejection of product claims for synthetic polyisoprene having essentially the molecular structure of natural Hevea rubber. Applicants appealed. The Court of Customs and Patent Appeals, Lane, J., held that the Board erred in affirming a multiplicity rejection and in its application of the word 'synthetic' as used in some of the claims, but that antedating affidavits were insufficient to remove a prior patent as a reference with respect to certain other claims relating to a gelfree product.

Decision of Board affirmed as to certain claims and reversed as to certain other claims.

West Headnotes

[1] Patents ⇨101(5)
291k101(5) Most Cited Cases

Patent applicant should be allowed to determine necessary number and scope of his claims, provided he pays required fees and otherwise complies with statute, and Patent Office Board of Appeals erred in rejecting claims as "unnecessary." 35 U.S.C.A. § 112.

[2] Patents ⇨101(6)
291k101(6) Most Cited Cases

Where each appealed claim was relatively brief and clear in its meaning, though reciting inherent properties of polymer, Patent Office Board of Appeals erred in rejecting claims as tending to obscure invention and thereby failing to comply with statute. 35 U.S.C.A. § 112.

[3] Patents ⇨101(5)
291k101(5) Most Cited Cases

Where product claims did not recite presence or absence of any impurities other than naturally occurring ones, and there was no convincing evidence of record that presence or absence of such impurities would affect product, claims were not overly broad for failing to contain limitation as to catalytic impurities. 35 U.S.C.A. § 112.

[4] Patents ⇨51(1)
291k51(1) Most Cited Cases

It was not required that product shown in antedating affidavits should, standing alone, support broader claims. Patent Office Practice Rules, rule 131, 35 U.S.C.A. App.

[5] Patents ⇨62(1)
291k62(1) Most Cited Cases

Antedating affidavits were not insufficient merely because they did not show composition which reference showed. Patent Office Practice Rules, rule 131, 35 U.S.C.A. App.

[6] Patents ⇨62(1)
291k62(1) Most Cited Cases

Where patent applicants showed in their antedating affidavits the manufacture of claimed product by use of lithium-based catalysts and reference showed its preparation using other catalysts, but applicants possessed claimed product as fully as inventor who obtained reference patent, and before date of reference patent reference was overcome as to such claims. 35 U.S.C.A. §§ 102, 102(e), 103; Patent Office Practice Rules, rule 131, 35 U.S.C.A. App.

[7] Patents ⇨62(1)
291k62(1) Most Cited Cases

Where antedating affidavits did not show possession of a gel-free product prior to date of reference patent, affidavits were insufficient to overcome patent as reference, for claims reciting substantially gel-free polymer.. Patent Office Practice Rules, rule 131, 35 U.S.C.A. App.

[8] Patents ⇨101(2)
291k101(2) Most Cited Cases

Word "synthetic" as used in claims for synthetic product was not applicable to purified natural product of reference patent. 35 U.S.C.A. § 103.

[9] Patents ⇨16.4
291k16.4 Most Cited Cases
(Formerly 291k18)

Method of making synthetic product having essentially molecular structure of natural rubber was not "prima facie obvious" from reference patent for elimination of impurities from natural rubber. 35 U.S.C.A. § 103.

[10] Patents ⇨101(5)
291k101(5) Most Cited Cases

Statute requiring specification in patent application does not require that claims define invention but that they define subject matter which applicant regards as his invention, and

this simply requires that applicant set definite boundaries on patent protection sought. 35 U.S.C.A. § 112.

[11] Patents ⇐101(5)
291k101(5) Most Cited Cases

Rejection of claims for patent as being broader than invention clearly described in specification is really assertion that specification is insufficient to support claims of breadth sought, and proper statutory basis for such rejection is requirement that specification contain written description of invention and of manner and process of making and using it. 35 U.S.C.A. § 112; Patent Office Practice Rules, rule 193(b), 35 U.S.C.A. App.

[12] Patents ⇐101(6)
291k101(6) Most Cited Cases

Claims were not indefinite for use of negative limitation excluding characteristics of prior art products, where each recited limitation was definite. 35 U.S.C.A. § 112.

[13] Patents ⇐101(6)
291k101(6) Most Cited Cases

Word "synthetic" as used in product claims had reasonably precise meaning, excluding from scope of claims any purified natural product, and though use of word alone did not make claimed composition new, word was not indefinite and did not provide basis for rejecting claims for failure to point out and distinctly claim subject matter which applicants regarded as their invention. 35 U.S.C.A. § 112.
Patents ⇐328(2)
291k328(2) Most Cited Cases

3,114,743. Cited as prior art.
****899 *960** Edward S. Irons, Mary Helen Sears, Irons, Birch, Swindler & McKie, Washington, D.C., Stanley M. Clark, H. N. Harger, Akron, Ohio, attorneys of record, for appellants.

Joseph Schimmel, Washington, D.C., for the Commissioner of Patents. Raymond E. Martin, Washington, D.C., of counsel.

Before RICH, Acting Chief Judge, ALMOND, BALDWIN, and LANE, Judges, and MATTHEWS, Senior Judge, United States District Court for the District of Columbia, sitting by designation.

LANE, Judge.

This appeal is from the decision of the Patent Office Board of Appeals, which affirmed the rejection of product claims 1-3, 5-8, 10-17, 19-22, 24-26 and 28- 31 in appellants' patent application serial No. 199,603, filed June 4, 1962, for 'Essentially Cis Rubbery Polyisoprene and Method for Making Same.' The application is a continuation-in-part of applications serial No. 503,396, filed August 24, 1955, and serial No. 605,438, filed August 21, 1956. Four method claims have been allowed.

THE DISCLOSURE

The application discloses a method of making a synthetic polyisoprene having essentially the molecular structure of natural Hevea rubber, i.e., at least 80% Cis-1, 4, not more than 10% Trans 1, 4, not more than 10% 3, 4, and practically no 1, 2 structure. The synthetic product will then have the advantageous properties of natural rubber but will not contain the proteins, soaps, resins and sugars which are disadvantageously present in natural rubber. The disclosed process of making the synthetic product involves the use of a catalyst which may be metallic lithium, a hydrocarbon lithium compound, a crystalline ***961** salt in admixture with colloidally dispersed lithium metal, a composite comprising either lithium metal or a lithium hydrocarbon in association with a fluorine-containing salt, or a Ziegler type catalyst. Information on selection and use of each of the catalysts is set forth in the specification but is unnecessary for an understanding of the issues here. Seventeen examples are disclosed in the specification to detail the use of the various types of catalysts.

THE INVENTION

Claim 1 is illustrative of the claims on appeal.

1. A synthetic homopolymer (of) isoprene combining the desirable properties of both Hevea and sulfur vulcanizable synthetic rubbers characterized by at least 80% Cis-1, 4, structure, not in excess of 10% Trans-1, 4 structure, not in excess of 10% 3, 4 structure, and essentially no 1, 2 structure, said homopolymer being free from the proteins, soaps, resins and sugars present in natural Hevea rubber.

The other appealed claims add one or more limitations to the subject matter of claim 1, and we shall discuss them in more detail later.

****900** PRIOR ART

Horne, U.S. patent 3,114,743, issued December 17, 1963, filed December 2, 1954, discloses a cis-1, 4 polyisoprene rubbery polymer which has essentially the same structure and physical properties as natural Hevea rubber. Horne states that all of the isoprene formed by his method is of the cis-1, 4 structure and that it is free from protein, soaps, resins and sugars. Applicants attempted to remove Horne as a reference by submitting affidavits under Rule 131.

The examiner and the board also applied Davis et al., Chemistry and Technology of Rubber, 1937, pp. 91-92, alone as a reference under 35 U.S.C. § 103. Davis discloses the structure of natural Hevea rubber and describes attempts to purify it.

THE EXAMINER

The examiner rejected all the appealed claims for undue multiplicity under 35 U.S.C. § 112 and required that applicants either reduce the number of claims to fifteen or select fifteen claims for further examination on the merits. Applicants traversed this rejection and provisionally elected fifteen claims for further prosecution. The examiner refused to withdraw the multiplicity rejection and continued to apply it to all claims. He also rejected all the claims for failing to define the invention and for obviousness in view of Davis. He further rejected claims 1, 3 and 5-8 for lack of novelty based on Horne, and the remaining claims for obviousness in view of Horne.

***962** THE BOARD

The board affirmed all of the examiner's rejections. We shall separately treat each affirmance and state our opinion with regard thereto.

OPINION

(a) Multiplicity

[1][2] The board stated that many of the claims recite 'only the obvious vulcanizate of the homopolymer, with varying recitations of its properties stemming from the negative recitation' appearing in claim 1. Other claims, said the board, merely give a somewhat more restricted range of percentages of the various structures in the polymer. The board agreed with the examiner that if the polyisoprene is adequately defined in each claim, then claims reciting the inherent properties of the polymer are unnecessary and tend to confuse the issue. The board held the number of claims to be unreasonable and to have the effect of obscuring the invention rather than pointing it out as required by 35 U.S.C. § 112. The board's affirmance of multiplicity rejection, therefore, is based upon the view that the many different definitions of appellants' invention were both unnecessary and confusing. We disagree on both points. It is rarely possible to determine necessity for narrower claims at the time of prosecution. An applicant often does not know all the prior art which may be asserted against his broader claims when he litigates his patent. Further, he is never sure that the broader claims will not be successfully attacked on other grounds when litigated in the courts. See e.g., Graver Tank & Mfg. Co. v. Linde Air Products, 336 U.S. 271, 69 S.Ct. 535, 93 L.Ed. 672 (1949). Moreover, there is no statutory authority for rejecting claims as being 'unnecessary.' For these reasons, an applicant should be allowed to determine the necessary number and scope of his claims, provided he pays the required fees and otherwise complies with the statute. This brings us to the board's view that the number of claims was so large as to obscure the invention, thereby failing to comply with the second paragraph of 35 U.S.C. § 112. Again we disagree. Each appealed claim is relatively brief and clear in its meaning. Examination of forty claims in a single application may be tedious work, but this is no reason for saying that the invention is obscured by the large number of claims. We note that the claims were clear enough for the examiner to apply references against all of them in his ****901** first action. We conclude that the board erred in affirming the multiplicity rejection.

(b) The rejections on Horne

We now come to the rejections under 35 U.S.C. § 102 and § 103 based on the Horne patent. Horne was cited under section 102(e) and applicants sought to remove the reference by submitting affidavits under Rule ***963** 131. The examiner found that the affidavits were insufficient in breadth to remove Horne as a reference against the claims. He considered the claims broad as against Horne in several respects which we shall separately treat.

[3] The first aspect of breadth considered by the examiner was that the claims contain no limitation as to catalytic impurities which he believed would be present in the product and would affect its properties. Horne used Ziegler type catalysts. The affidavits show appellants' use of lithium-based catalysts. The claims cover products containing either type impurity, and the examiner considered them broad for this reason. The board apparently agreed, pointing out that the type of catalyst used might result in significantly different products. Appellants disputed vigorously that their product contained any lithium end groups. We find it unnecessary to decide that question here, because there is no convincing evidence in the record that the presence or absence of such impurities would affect the product. Since the claims do not recite the presence or absence of any impurities other than the naturally occurring ones. we must conclude that such limitations are not essential to appellants' case for patentability. Appellants should not be required to show how various nonessential impurities could be added to the recited elements of their polymer. This is making a breadth problem where none exists.

[4][5][6] The second aspect of breadth considered by the examiner was the gel content of the product. It was the examiner's position that the product shown in appellants' Rule 131 affidavits 'is not the same polymer disclosed by Horne and does not support the broad claim.' This

conclusion was derived from the fact that the product shown in the attachments to the affidavits was stated therein to contain 'considerable hard, non-dispersable gel,' whereas Horne states that his product is adaptable to be gel-free. Although the board nowhere mentioned this issue, we consider it to have been fairly raised by the examiner. It is necessary, in treating this issue, to separate the claims which contain no limitation as to the presence or absence of gel from the claims which recite that the product must be 'substantially gel-free.' [FN1]

> FN1. The latter group comprises claims 2, 7, 16, 21, 25 and 30.

As to the first group, the examiner's contention that the product shown in the affidavits, called CPP 1196, [FN2] does not 'support the claim' is irrelevant. It is uncontested that CPP 1196 is in fact a compound falling under this first group of claims. The fact that it alone would not support the broader claims is of no significance. See In re Clarke, 356 F.2d 987, 991, 53 CCPA 954, 960 (1966). ***964** Turning to the examiner's argument that the affidavits are insufficient because they do not show the composition which the reference shows, this court rejected such a test in Clarke, supra, and stated instead that 'antedating affidavits must contain facts showing a completion of 'the invention' commensurate with the extent the invention is shown in the reference, whether or not it be a showing of the identical disclosure of the reference.' It is clear those claims which recite nothing about gel do not define an invention predicated for patentability upon the presence or absence or gel. With regard to the recited elements of these claims, we believe appellants have shown as much as Horne shows. Appellants show in ****902** their affidavits the manufacture of the claimed product by the use of lithiumbased catalysts. Horne shows its preparation using Ziegler catalysts. Appellants possessed the claimed product as fully as Horne did, and before the Horne date. Horne is therefore overcome as a reference as to these claims. [FN3] See In re Rainer, 390 F.2d 771, 55 CCPA 853 (1968).

> FN2. The examiner referred to this product as CP 1198. This was apparently inadvertent, since we find no other reference in the record to a product so designated.

> FN3. It might be noted here that the examiner mentioned other aspects of breadth, such as molecular weight and molecular weight distribution. Since these assertions were not supported by reference to appropriate evidence of record, we consider any issues based thereon not to have been raised below.

[7] We now consider the claims reciting a 'substantially gel-free' polymer. Here, of course, we cannot ignore the significance of the fact that appellants' affidavits do not show possession of a gel-free product. The issue is whether Horne enables persons of ordinary skill to make the gel-free product. The Horne patent is far from clear on this point. It states, in part:

The process described herein is adaptable to give a linear polyisoprene rubber which * * * is free of extremely high molecular fractions or cross-linked fractions, called gel, such as are present in natural rubber.

The examiner believed Horne's product to be gel-free. His opinion is supported by Horne's example 1, which states that a clear solution of the reaction product in heptane is obtained, which upon precipitation, washing and drying 'is found to possess a tackiness equivalent to that of milled natural rubber * * *.' Milling is one of the ways of removing the gel from natural rubber. The last-quoted portion of Horne would therefore indicate that the product has no substantial gel. Moreover, while appellants have pointed out the lack of complete clarity in Horne's statement concerning gel, they have not argued that Horne's example 1 does not in fact produce a gel-free product. On the basis of the record before us, we conclude that the examiner was correct in his view that Horne discloses a substantially gel-free product. Since appellants' affidavits do not show their possession of such a product prior to the Horne date, we must affirm the board's decision as to claims 2, 7, 16, 21, 25 and 30.

***965** (c) The rejection on Davis

The examiner rejected all of the fully prosecuted claims as unpatentable over Davis, under 35 U.S.C. § 103. The examiner acknowledged that Davis does not show a complete removal of all impurities from natural rubber. His position was that 'the pure compound is so similar to the impure compound (no non- obvious utilitarian differences accountable to the purity level have been shown) as to be prima facie obvious.' The board affirmed the rejection 'for the reasons fully set forth by the Examiner,' adding that the word synthetic in the claims is applicable to natural rubber 'from which the impurities have been extracted in Davis.'

We do not think that Davis is effective as a reference against any of the claims. [FN4] Davis describes the separate work of various researchers in removing proteins and resins from natural rubber. The description of each elimination attempt is brief, and a complete statement of results does not appear. Moreover, Davis nowhere mentions the elimination of sugars and soaps.

> FN4. From this point on we are discussing only the claims still in issue, i.e., claims 1, 3, 5, 6, 8, 10-15, 17, 19, 20, 22, 24, 26, 28, 29 and 31.

[8] We turn first to the board's view that the word 'synthetic'

as used in the claims is applicable to natural rubber from which impurities have been removed. We cannot agree that this is a reasonable construction of 'synthetic.' The dictionary meaning of the word as it pertains to chemistry is shown by the following:

Of pertaining to, or formed by artificial synthesis. Webster's New International Dictionary (1932). ****903** Noting or pertaining to compounds formed by chemical reaction in a laboratory, as opposed to those of natural origin. Random House Dictionary (1969).

'Synthetic rubber' is defined as

any of several substances similar to natural rubber in properties and uses, produced by the polymerization of an unsaturated hydrocarbon, as butylene or isoprene, or by the copolymerization of such hydrocarbons with styrene, butadiene, or the like. Random House Dictionary (s969).

The foregoing definitions nowhere mention or suggest to us that a purified natural product could properly be called 'synthetic.' Rather, the word connotes an artificially compounded or built-up product.

Moreover, to persons skilled in the rubber art the word 'synthetic' would not include a purified natural product. This is demonstrated in the Horne patent, wherein synthetic is defined as 'manmade.' The preliminary portions of appellants' specification lead to the same conclusion. The specification draws a sharp and consistent distinction ***966** between synthetic rubbers on the one hand and products made from natural rubber on the other.

In view of the foregoing, we must disagree with the board's position that the word 'synthetic,' as used in the claims, would be applicable to the purified natural product.

[9] We turn now to the examiner's view, adopted by the board, that the synthetic product is so similar to the natural product, purified to the extent allegedly shown in Davis, as to be 'prima facie obvious.' We would agree with this conclusion as a tentative one based on similarity of structure and gross characteristics. However, such tentative conclusions of obviousness are rebutted in those instances where there was, at the time the invention was made, no known or obvious method of making the claimed composition, or where the claimed composition is found to possess unexpected characteristics. At least the first situation is present in the case before us, since it cannot be said that a method of making the claimed synthetic product would be known or obvious from Davis. On the contrary, the record before us shows that years of effort in the art were required after Davis to find such a method. We conclude, therefore, that the rejection for obviousness based on Davis cannot be supported.

(d) The rejection for 'not properly defining the invention.'

[10] In the final rejection, the examiner stated that certain claims 'are rejected as not properly defining the invention (35 U.S.C. § 112).' He stated three bases for this conclusion, two of which have been removed through amendment. The remaining basis is the examiner's view, mentioned above, that applicant's polymers contain lithium end groups, which were not recited in the claims. Presumably this position is limited to the examples wherein appellants disclose the use of lithium-based catalysts. Such a ground of rejection cannot be sustained. Section 112 does not require that the claims define 'the invention,' whatever that would mean. It is apparently the second paragraph of that section which is in issue, and that paragraph requires that the claims define 'the subject matter which the applicant regards as his invention.' The meaning of this provision is simply that an applicant is required to set definite boundaries on the patent protection sought. The record before us amply demonstrates that appellants did not regard catalytic impurities as even being present in their products, much less regard such impurities as an element of their invention.

[11] The examiner's answer possibly shifted his statutory basis for the § 112 rejection, stating: 'The claims are rejected under 35 U.S.C. § 112 as being broader than that invention clearly described in the specification.' A breadth rejection such as this is really an assertion that the specification is insufficient to support claims of the breadth sought. ****904 *967** See In re Cavallito, 306 F.2d 505, 49 CCP A 1335 (1962). The proper statutory basis for such a rejection is the first paragraph of § 112. [FN5] In response to this possible shift in ground by the examiner, appellants submitted a reply brief under Rule 193(b). The board refused to consider the reply brief and held that the examiner's answer did not raise a new point of argument. We are not sure whether an attack on the specification was being made. If it was, appellants were deprived of an opportunity to contest this new basis for the § 112 rejection before the board. Further, the board's opinion makes no reference to insufficiency of disclosure. Accordingly, we shall not consider it to be in issue before us.

> FN5. See In re Borkowski (PA 8214) Cust. & Pat.App., 422 F.2d 904 decided concurrently herewith.

[12] We turn, therefore, to the board's affirmance of the rejection for indefiniteness under the second paragraph of § 112. The board set forth two bases for concluding that the claims were indefinite. The first was that the use of a negative limitation excluding the characteristics of the prior art products causes the claims to read on a virtually unlimited number of materials, many of which 'might be the full equivalents in their effects of those excluded.' We fail to

see how this renders the claims indefinite. The complaint seems to be that a very large number of substances are encompassed by the claims, through the possible addition of unrecited impurities. The scope of the claim is still definite, however, because each recited limitation is definite.

[13] The board's second basis for concluding indefiniteness was that the claims

(read) better upon the natural product from which the named substances have been removed than upon that prepared by the disclosed method of this application, which obviously never had these substances present to contend with in the first place.

With this we disagree for the reasons stated above with regard to the Davis reference. Appellants have excluded from the scope of their claims any purified natural product by the recitation 'synthetic.' This word, as we have shown above, has a reasonably precise meaning and therefore does not render the claims indefinite. It is not contended, and we are not holding, that the word synthetic alone makes the claimed composition new. We are holding that, as used here, the word is not indefinite and does not provide a basis for rejecting the claims under the second paragraph of § 112. We conclude that the board erred in affirming the rejection under 35 U.S.C. § 112.

The decision of the board is affirmed as to claims 2, 7, 16, 21, 25 and 30, and reversed as to claims 1, 3, 5, 6, 8, 10-15, 17, 19, 20, 22, 24, 26, 28, 29 and 31.

***960** Modified.

422 F.2d 897, 57 C.C.P.A. 959, 164 U.S.P.Q. 636

END OF DOCUMENT

United States Patent [19]

Bazzano

[11] Patent Number: **5,183,817**

[45] Date of Patent: **Feb. 2, 1993**

[54] **COMBINATIONS OF RETINOIDS AND MINOXIDIL-TYPE COMPOUNDS FOR HAIR GROWTH**

[76] Inventor: **Gail S. Bazzano, 4506 Avron Blvd., Metairie, La. 70006**

[21] Appl. No.: **283,646**

[22] Filed: **Dec. 13, 1988**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 136,525, Dec. 22, 1987, abandoned, which is a continuation of Ser. No. 463,146, Feb. 2, 1983, abandoned, which is a continuation-in-part of Ser. No. 235,169, Feb. 17, 1981, abandoned, and a continuation-in-part of Ser. No. 318,607, Nov. 9, 1981, abandoned, and a continuation-in-part of Ser. No. 368,730, Jun. 9, 1982, abandoned, and a continuation-in-part of Ser. No. 414,854, Sep. 3, 1982, abandoned.

[51] Int. Cl.[5] **A61K 31/505; A61K 31/07**

[52] U.S. Cl. **514/256**; 514/725; 514/880

[58] Field of Search 514/725, 256, 313

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3,464,987	9/1969	Ursprung et al.	514/880
3,729,568	4/1973	Kligman	514/859
3,882,244	5/1975	Lee	424/70 UX
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4,139,619	12/1979	Chidsey	514/725 UX
4,170,229	10/1979	Olson	424/70 UX
4,220,772	9/1980	Muller et al.	544/255
4,232,438	3/1982	Peck	424/70 UX
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4,287,338	9/1981	McCall	544/123
4,304,787	12/1981	Gander et al.	424/70 UX
4,333,924	6/1982	Bowley et al.	424/70 UX

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Primary Examiner—Dale R. Ore

Attorney, Agent, or Firm—Panitch Schwarze Jacobs & Nadel

[57] **ABSTRACT**

Increase in the rate of hair growth, stimulation of hair follicles to produce new hair growth, prolongation of the anagen phase of the hair cycle, conversion of vellus hair to growth as terminal hair, and treatment of alopecias due to organic dysfunction of the hair follicle is attained in mammalian skins by either oral administration or by topical application to the skin, hair and/or hair follicles of the mammal of effective amounts of a retinoid, particularly retinoic acid, and a minoxidil-type compound. The combination may be administered or applied alone or with other adjunctive compounds including vitamins, such as Vitamin D_3, hormones, and/or antiandrogens.

30 Claims, No Drawings

102.

COMBINATIONS OF RETINOIDS AND MINOXIDIL-TYPE COMPOUNDS FOR HAIR GROWTH

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of copending application Ser. No. 136,525, filed Dec. 22, 1987, now abandoned, which in turn is a continuation of Ser. No. 463,146, filed Feb. 2, 1983, now abandoned, which in turn is a continuation-in-part of applications Ser. No. 235,169, filed Feb. 17, 1981; Ser. No. 318,607, filed Nov. 9, 1981; Ser. No. 386,730, filed Jun. 9, 1982; and Ser. No. 414,854, filed Sep. 3, 1982, all now abandoned. This application is also related to my co-pending application Ser. No. 283,649, filed concurrently herewith, entitled "Use Of Retinoids And Compositions Containing Same For Hair Growth".

FIELD OF INVENTION

This invention relates to the use of synergistic combinations with minoxidil (2,4,-diamino-6-piperidinopyrimidine-3-oxide) or certain of its derivatives or analogs in order to increase the rate of and stimulate growth of hair on mammalian skins, particularly human scalp hair to prolong the anagen phase of the hair cycle, to convert vellus hair to growth as terminal hair, and to treat certain types of alopecias.

BACKGROUND OF THE INVENTION

A normal characteristic of hair growth in mammals, including humans, is that in most cases, the rate of hair growth and the length of its growth cycle are reduced with age. Those phenomena are common to all mammals with rare exceptions, and they must be differentiated from true male pattern alopecia, which is caused by target organ sensitivity to androgens.

Several factors may influence the rate of hair growth. These factors include race, sex, age, geography, season of the year, nutrition and hormones. See Myers, R. J. and Hamilton, J. B. "Regeneration and rate of growth of hairs in man" *Ann. N.Y. Acad. Sci.* 53:562–568 (1951); Hamilton, J. B. "Age, sex and genetic factors in the relation of hair growth in man: A comparison of Caucasian and Japanese populations" *The Biology of Hair Growth* (Ed. Montagna, W. and Ellis, R. A.), Academic Press Inc., New York, pp. 400–433 (1958); Yano, S. "Rate of hair growth" *Hifu to Hinyo* 4:546–552 (1936); Maeda, I. "Study on the cuticula of hair: (III) Relation between the cuticula and rate of the growth of human hair" *Jyuzenkai-Zasski.* 43:1298–1304 (1938); Trotter, M. "The resistance of hair to certain supposed growth stimulants" *Arch. Dermatol. and Syphilol.* 7:93–98 (1923); Pinkus, F. "Zur Kenntnis der Lebensdauer der menschlichen terminal haare" *Z. Morphol. und Anthropol.* 24:256–269 (1924); Ono, M. "Studies on the hair growth of beard and scalp hair (1st report) Influencing factor in the rhythms of hair growth" *J. Physiol. Soc. Japan* 25:254–261 (1963).

Various preparations have heretofore been proposed for the treatment of male pattern baldness. It is also a matter of common knowledge, however, that none of the so-called "hair growth formulae" have proven to be very efficacious.

In contrast to most epithelial structures, the hair follicle does not grow continuously throughout its life, but passes through a cycle called the pilar cycle. The pilar cycle comprises essentially three phases—namely, the anagen or growth phase during which hair is produced, normally lasting about three to seven years; the catagen phase when growth stops and the follicle atrophies, lasting about three to four weeks; and the telogen phase, which is a rest period for the follicle during which the hair progressively separates and finally falls out, and normally lasting about three to four months. Normally 80 to 95 percent of the follicles are in the anagen phase, less than 1 percent being in the catagen phase, and the rest being in the telogen phase. Whereas the telogen phase hair is uniform in diameter with a slightly bulbous, non-pigmented root, the anagen phase hair has a large colored bulb at its root.

Alopecia results when the pilar cycle is disturbed, resulting in excessive hair loss. The most frequent phenomenon is a shortening of the hair growth phase due to cessation of cell proliferation. This results in an early onset of the catagen phase, and consequently a large number of hairs in the telogen phase during which the follicles are detached from the dermal papillae, and the hairs fall out. This shortening of the growth or anagen phase of the pilar cycle may have different origins, among which are very diverse pathological origins such as febrile conditions, mental stresses, hormonal problems (such as androgenetic alopecia due to male hormones) and secondary effects of drugs. Alopecia may also be due to age and to a slowing down of mitotic activity. This dysfunction of the biological mechanism of hair growth leading to alopecia may be regarded as a disease. While there are other causes of alopecia such as greasy or oily scalp due to seborrhea and the dandruff accompanying it, the present invention is not directed to treating these extraneous causes of alopecia, but rather to treating the organic dysfunction of the hair follicle.

German Patent No. 2758484 discloses certain chemical preparations for treatment of scalp to prevent baldness. These preparations contain bile compounds as the active ingredients and also include pro Vitamin A or tretinoin. The active ingredient is a product obtained from gall or a derivative thereof such as chenodeoxycholic acid, urodoxy cholic acid and their salts or derivatives.

Another patent is Olsen U.S. Pat. No. 4,140,229 citing the use of Vitamin A-containing crystal clear, transparent, aqueous, sprayable emulsions for reducing itching and flaking of common dandruff and seborrhea. As stated in its abstract, in some instances, the use of such emulsions reduced excessive falling hair. It does not purport to stimulate hair growth. It simply teaches a method of conditioning hair and scalp to effect relief from dandruff symptoms. The only pertinent example in Olson is discussed under Case History No. 3 of Example IV wherein the "Spray-on-Brush-in-Solution" contained Vitamin A palmitate and seven other ingredients. All that is disclosed is that "the daily loss of head hair was reduced to approximately 10 to 20."

Knight British patent specification No. 1,466,062 discloses a cosmetic composition containing tocopherol and retinoic acid as a cosmetic preparation which can be used on the skin or as a hair cleaning or hair dressing agent. This multi-purpose cosmetic composition allegedly prevents age spots, and is claimed to be good for clearing the scalp of dandruff. It appears that, during clearing of the scalp of dandruff with this composition, the scalp can become healthier, hair loss is reduced, and

hair growth can be obtained. A specific treatment for androgenetic alopecia or male pattern alopecia is not suggested by this disclosure. The use of retinoids to alter the hair follicle growth rate or to prolong the anagen phase of the hair cycle is also not disclosed or discussed by Knight. Knight is claiming a cosmetic lotion for cleaning the scalp. Common dandruff and seborrhea or seborrheic dermatitis (seborrhea is the production of excess sebum and seborrheic dermatitis is an irritation of the scalp), as well as age spots, are the topic of this patent, and the composition used is a combination of two ingredients (Vitamin E and retinoic acid) in a cosmetic base.

There is a reference in the literature to the treatment of monilethrix using tretinoin (retinoic acid). Monilethrix is a vary rare genetic disease in which the hair shaft is defective and the hair is sparse and fragile. Topical application of retinoic acid improved the symptoms of this genetic defect. Hernandez-Perez, E. "Tretinoin therapy for monilethrix" *Archives of Dermatology* 109:575-576 (1974).

The use of retinoic acid in many disease conditions has been recently reviewed in the *Journal of the American Academy of Dermatology* by Haas and Arndt, "Selected therapeutic applications of topical tretinoin" 15:870-877 (1986). The review article in the May 1981 *Journal of the American Academy of Dermatology*, by Thomas, et al. also gives a list of the known uses of retinoic acid, but the treatment of alopecia or androgenetic alopecia is not listed.

There are no references of which I am aware for the use of retinoids in altering the rate of hair growth and treating alopecias, such as androgenetic alopecia. In fact, quite the opposite is the case, and the literature is full of references to hair loss caused by the toxic use of retinoids in high concentrations. References to hair loss caused by retinoids include W. Bollag and A. Matter, "From Vit A to Retinoids in Experimental and Clinical Oncology", p. 9-23, *Modulation of Cellular Interactions by Vitamin A and Derivatives, (Retinoids)* (Eds. Luigi M. DeLuca, Stanley S. Shapiro) Annals of New York Academy of Sciences, Vol. 359 (1981) and *Retinoids: Advances in Basic Research and Therapy* (Eds. C. E. Orfanos) Springer-Verlag (1981)—See articles "Aromatic Retinoids in Psoriasis", p. 165-173, S. Jablouska, et al.; and "Treatment of Severe Forms of Psoriasis and Retinoic Acid Derivatives", J. C. Gatti, et al., p. 185-191.

One compound, minoxidil, a potent anti-hypertensive compound, has been found to promote hair growth when applied topically to the scalp, as discussed in U.S. Pat. No. 4,139,619 and 4,596,812 to Chidsey et al. Minoxidil is recognized as being somewhat effective in producing new vellus hair growth and sparse terminal hair growth in a preselected group of subjects. However, its effect is far from satisfactory in most subjects.

BRIEF SUMMARY OF THE INVENTION

According to the invention it has been found that retinoids or mixtures thereof in combination with minoxidil and/or minoxidil-type compounds are synergistically effective in stimulating or increasing the rate at which hair grows on mammalian skin, prolonging the anagen phase of the hair cycle, converting vellus hair to terminal hair growth, and treating alopecias due to organic dysfunction of the hair follicle by topical application to the hair and hair follicles and to the skin adjacent thereto. Preparations such as lotions, creams, shampoos, and the like containing the aforementioned compounds as the active ingredients, can be applied topically to the skin, hair and/or follicles for this purpose. Oral administration of the retinoids may also be used. Other adjunctive compounds which may be included in the compositions of the invention include vitamins, such as Vitamin D_3, hormones, and antiandrogens. The invention also includes the topical or oral administration of retinoids to fur bearing animals or birds to increase the rate of hair growth and/or retard shedding or molting.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

Retinoids have been shown to cause elevated DNA synthesis in keratinocytes in cell culture. Retinoids can also be shown to increase the turn-over time of epidermal cells in cell culture experiments as well as in vivo experiments with human subjects. As disclosed in my copending application Ser. No. 283,649, the present inventor has discovered that the cells of the hair follicle, particularly the keratinocytes, can be stimulated by retinoids. When tested experimentally, the retinoids caused the cells of the dermal papillae and the keratinocytes, as well as cells of the root sheath, to incorporate more tritiated thymidine into DNA and to reproduce at a more rapid rate than untreated cells from other hair follicles. This stimulation by the retinoid compounds ultimately causes the entire hair follicle to become more activated and the mitotic index, as measured by thymidine-H^3 incorporation into DNA, to rise. Therefore, the individual scalp hairs can be shown to grow at an increased rate, and the anagen phase is prolonged.

A major problem in influencing alopecia is to revascularize the area of alopecia and initiate the primary new hair growth. Retinoic acid and its derivatives and the other retinoid compounds have been shown to give excellent percutaneous absoprtion and to be very active on the keratinizing cells of the skin, including the hair follicle. However, it is difficult for retinoids alone to revascularize the area of the pilosebaceous apparatus.

Studies have shown that minoxidil, a potent antihypertensive medication and peripheral vasodilator, can increase the rate of hair growth on the body when taken systemically, particularly in areas of the limbs and facial areas, possibly due to vasodilatory properties. Further studies have suggested that minoxidil may be effective in initiating and promoting vellus hair growth on the scalp of individuals with alopecia. However, minoxidil may not able to sustain the growth of terminal hairs from vellus hairs on the scalp. In the majority of subjects with alopecia, terminal hair growth on the scalp may not be initiated or sustained by the topical application of minoxidil nor by its systemic administration.

Minoxidil has been shown to prolong the life of keratinocytes in culture and extend the time after confluence that cells can be subcultured. These data suggest that the mechanism by which minoxidil exerts its effect is that the drug reduces the rate at which cells are lost from the germinative pool and hence slows senescence. See J. Kubilus et al., "Effect of Minoxidil on Pre- and Postconfluent Keratinocytes," *Journal of the American Academy of Dermatology*, 16:648 (1987). Vascular effects alone do not appear to be a sufficient stimulus for hair growth, particularly in an area affected by alopecia. As described in my copending application Ser. No. 283,649, the disclosure of which is incorporated herein by reference, retinoids can stimulate and increase the

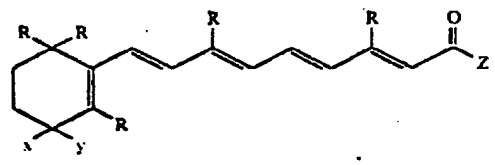
growth in both males and females and can prolong the anagen phase of the hair cycle, as well as converting vellus to terminal follicles. The mechanism of action of the retinoid compounds is believed to be through the initiation and activation of increased cell turnover and cell differentiation, i.e., compounds which of themselves can initiate the differentiation of cells of the pilosebaceous apparatus which eventually form the hair follicle and become terminal hairs.

Because of the advanced state of scalp thinning and atrophy of the pilary portion of the pilosebaceous apparatus, it is difficult to initiate hair growth from areas of advanced male pattern alopecia. Retinoid compounds sustain and promote hair growth in areas where hair is present to some extent.

The present invention combines the use of retinoid compounds with minoxidil, or its analogs or derivatives or minoxidil-type compounds (hereinafter collectively referred to simply as "minoxidil"). The stimulatory actions of both compounds can synergistically promote each others' effect. Retinoids can initiate cell growth and differentiation (not initiated by minoxidil), and minoxidil can promote the vasodilatory and mitogenic action not obtained with the retinoids. While neither compound alone may have profound effects on advanced alopecias, in combination the compounds are very effective as promoters of new hair growth in areas of alopecia.

The net result of application of minoxidil and retinoids is initiation and production of new hair growth and conversion of vellus to terminal hair growth, i.e., the increase in size from a vellus to a terminal hair and the continued and more prolonged maintenance of the hair in the anagen phase. As noted previously, this effect is obtained not merely as the addition of two compounds, but as synergism, i.e., the combination of these substances in the present invention produces an effect which cannot be produced by either compound separately under conditions of its use and, therefore, represents a major advance in the treatment of alopecia.

Suitable retinoid active ingredients for use in this invention include derivatives of retinoic acid (Vitamin A acid or tretinoin) which may be represented by the following formulae:



wherein R is hydrogen or a lower alkyl group, X is individually hydrogen and Y is individually hydrogen or a hydroxy group, or X and Y together form oxo, and Z is alkoxy, amide, alkylamide, hydroxy, nitro, or other suitable terminal groups. Also included by the above formula are pharmaceutically accepted salts thereof.

Further, the basic formula may include the dehydro, dihydro, or anhydro forms, such as the 7,8-dehydro and 5,6-dihydro forms, of retinoic acid as well as all of the stereoisomeric forms thereof, such as the 9-cis; 9,13-dicis; 13-cis; 11-cis; 11,13-dicis; etc. Examples are shown as follows:

13-cis-retinoic acid

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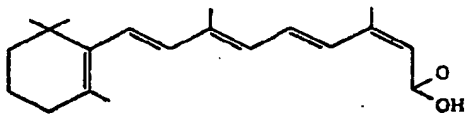
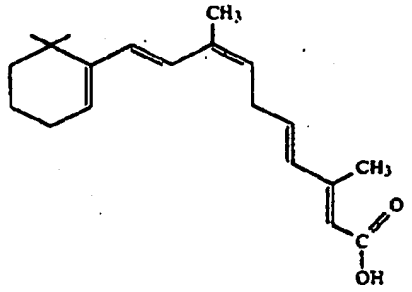
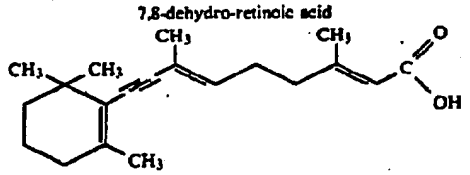


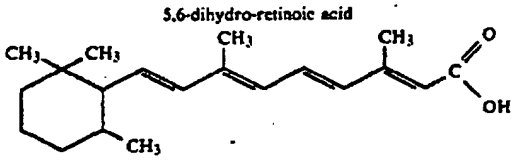
9-cis-retinoic acid



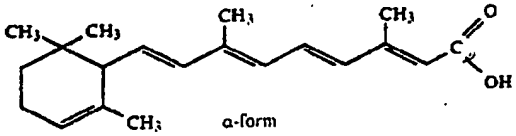
7,8-dehydro-retinoic acid



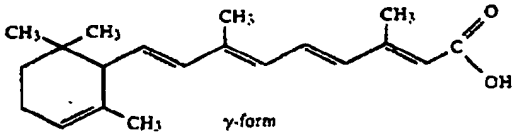
5,6-dihydro-retinoic acid



The anhydro forms may be represented by the following compounds:

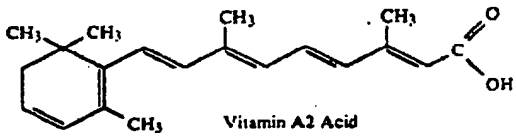


α-form

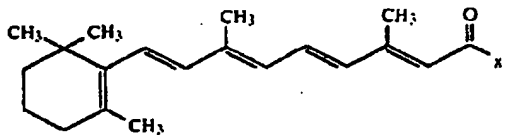


γ-form

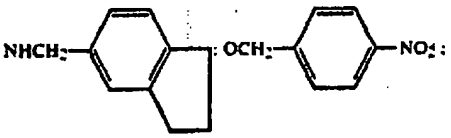
Suitable retinoid analogs and derivatives useful in the invention have the following general formulae wherein the side chain, the ring, or both, may be altered:

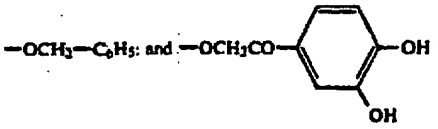


Vitamin A2 Acid



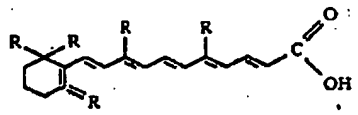
wherein X is a member selected from the group consisting of: $-OHCH_2CONH_2$: mixed $-OCH_2CH(OH)CH_3$ and $-OCH(CH_3)CH_2OH$; $-OCH$; as well as



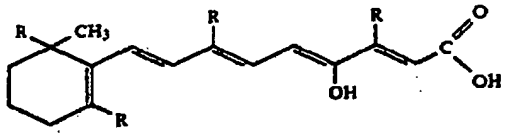


These compounds as well as other alkoxy and amide compounds can be active as they can be hydrolyzed to retinoic acid and other active compounds in the body. However, their activity may not be as direct as all-trans retinoic acid.

Other suitable retinoid compounds useful in the invention include α-hydroxy retinoic acid represented by the formula:

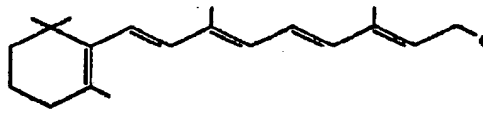


and the C_{22}-analog of retinoic acid represented by the following general formula:

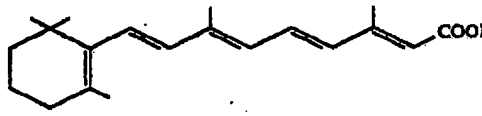


wherein R in both of the above formulae are lower alkyl radicals, preferably methyl groups.

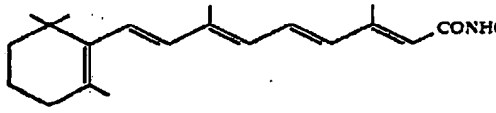
Other structurally modified retinoids which, to some degree, exhibit the activity of retinoic acid for hair growth purposes can be presented by the following general formulae:



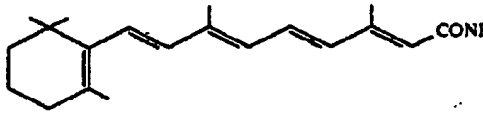
retinyl acetate



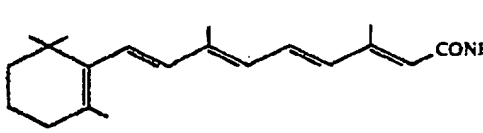
(all-E)-retinoic acid



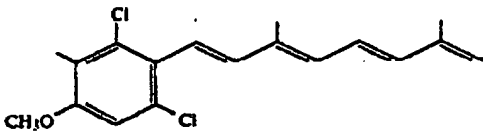
Retinoic Acid Ethyl Amide

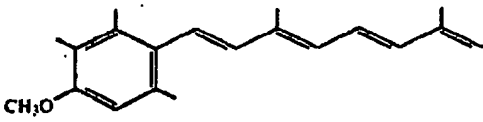


Retinoic Acid 2-Hydroxyethyl Amide



Retinoic Acid p-Hydroxyphenyl Amide





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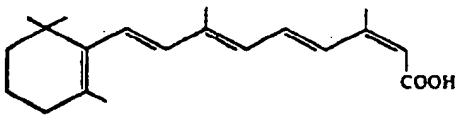
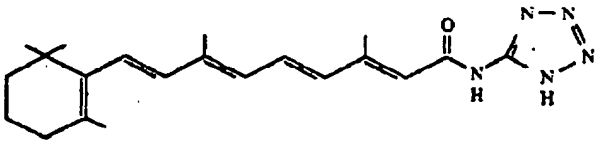


(13Z)-retinoic acid



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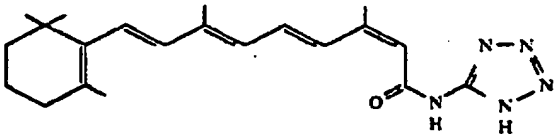

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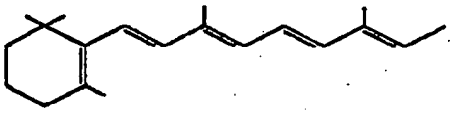
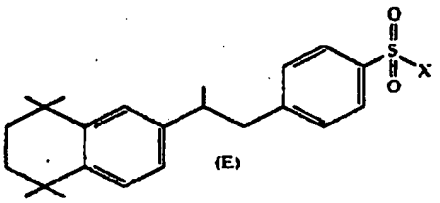
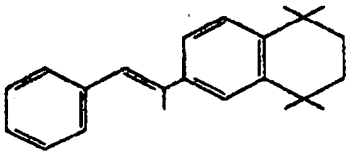


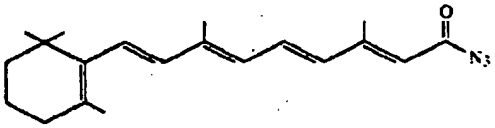
35739-BASF



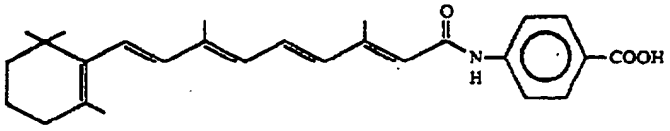
(E)



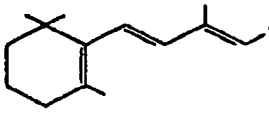
arotinoid



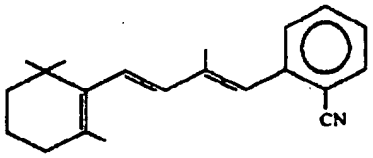
36591-BASF



35681-BASF



36592-BASF



36663-BASF

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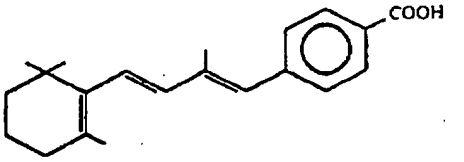
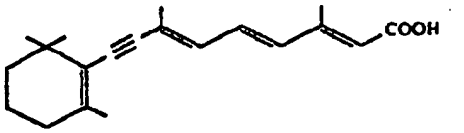
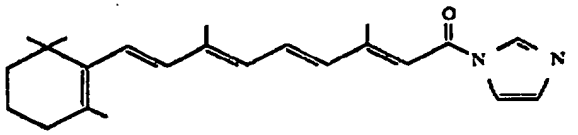


37400-BASF

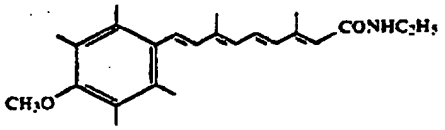


35684-BASF

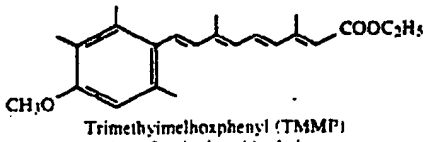


(all-E)-N-(1-imidozolyl)-retinamide

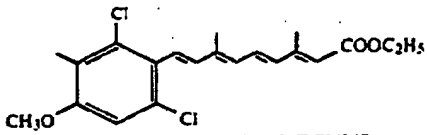
Still other useful analogs and derivatives of retinoic acid and retinoids include the following compounds:



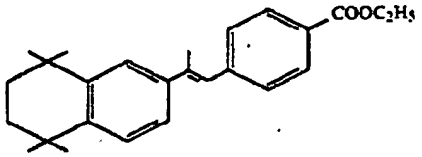
Trimethylmethoxphyenyl (TMMP) analog of retinoic acid ethylamide (Motretin)



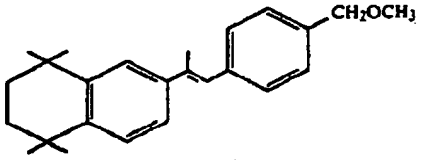
Trimethyimelhoxphenyl (TMMP) analog of retinoic acid ethyl ester (Etretinate)



Dichloromethylmethoxphenyl (DCMMP) analog of retinoic acid ethylester



Arotinoid ethyl ester



Arotinoid

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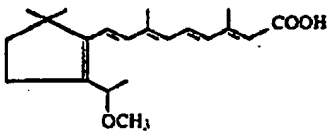
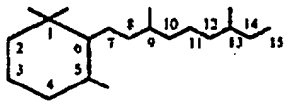
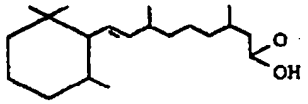


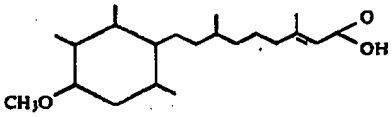
1-Methoxyethyl-cyclopentenyl analog of retinoic acid



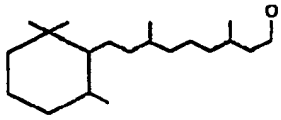
Axerophthene



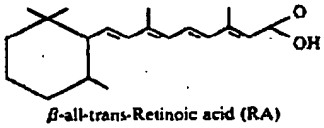
13-cis-Retinoic acid



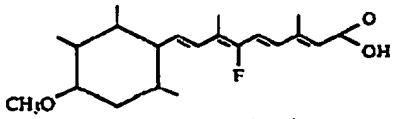
Trimethylmethoxyphenyl



Retinal



β-all-trans-Retinoic acid (RA)



10-Flouro-TMMP analog of RA

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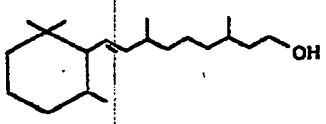
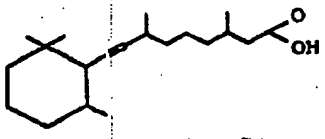
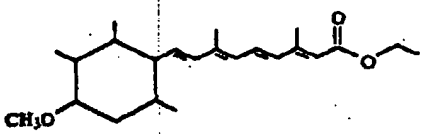


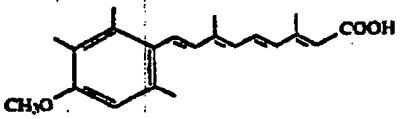
Retinol

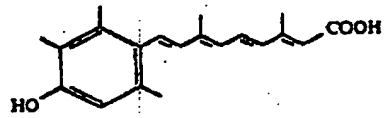


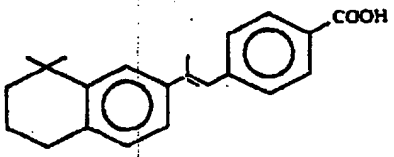
7,8-Dehydro analog or RA

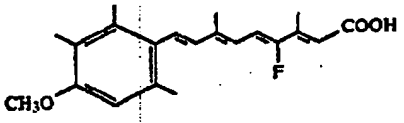


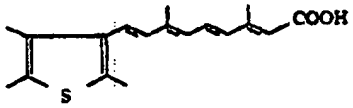
TMMP analog of ethyl retinoate

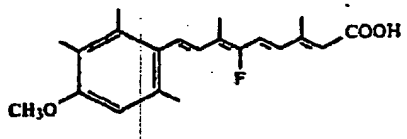


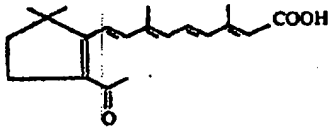












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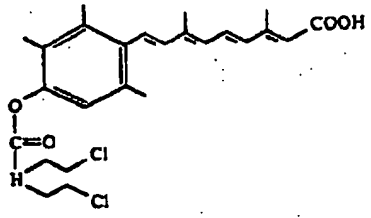

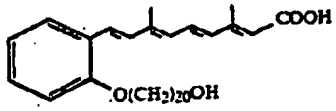

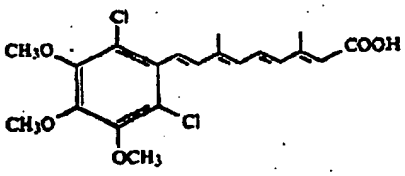

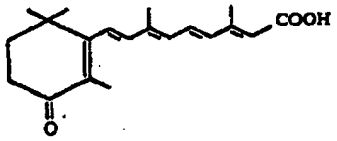

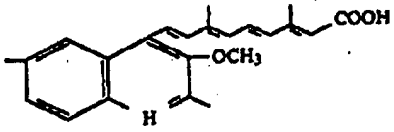

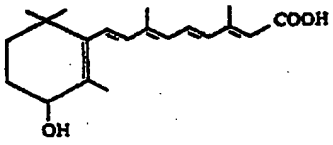

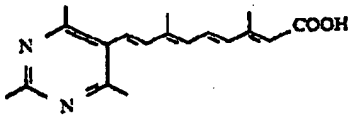

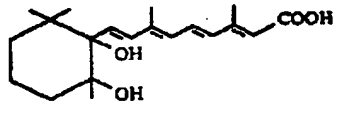

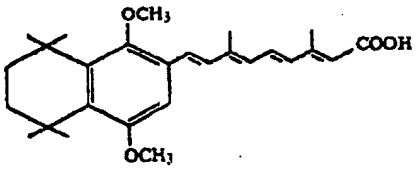

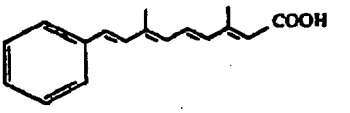

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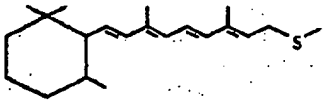
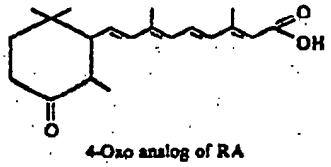
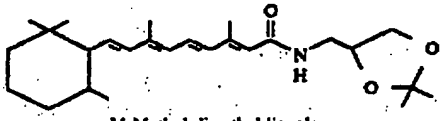


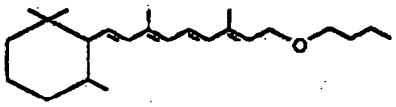
Retinyl methylthioether



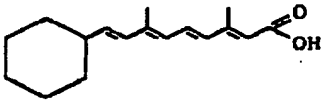
4-Oxo analog of RA



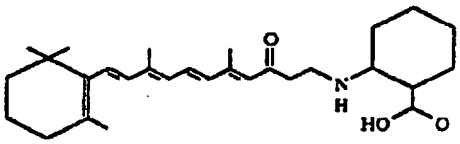
M-Methyl-dimethyldioxolan-retinomide



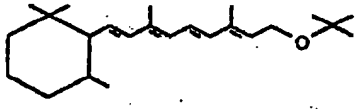
Retinyl n-butyl ether

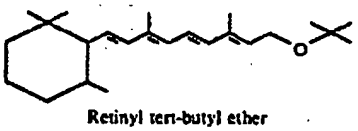


Phenyl analog of RA

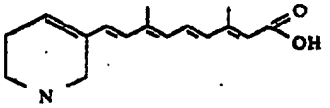


N-(O-Carboxyphenyl)-retinomide

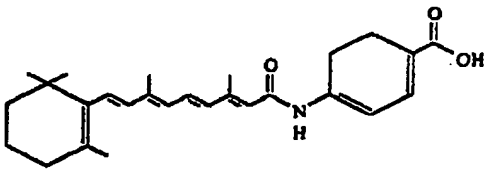




Retinyl tert-butyl ether



Pyridyl analog of RA



N-(p-Carboxyphenyl)-retinomide

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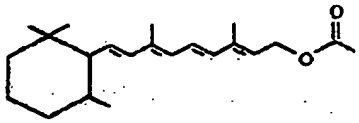
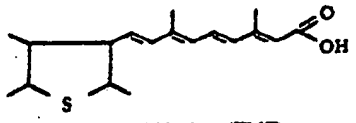
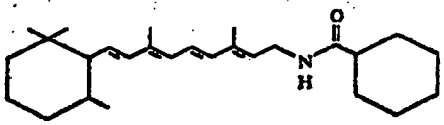


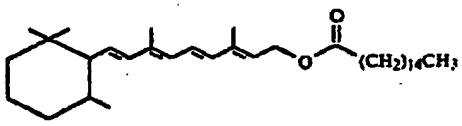
Retinyl acetate



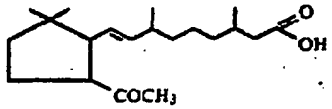
Trimethylthiophene(TMT) analog of RA



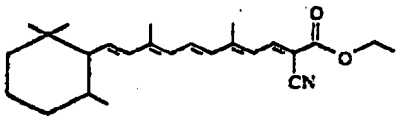
N-Benzoyl-retinylamine



Retinyl palmitate

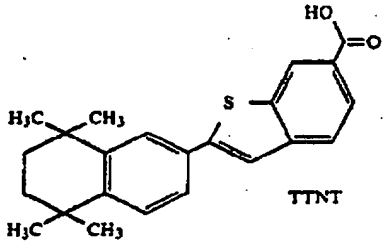


Dimethylacetyl cyclo-



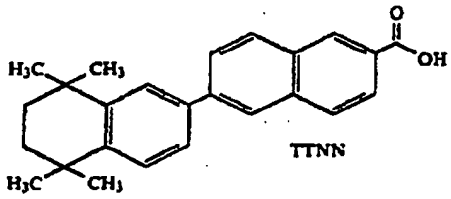
Retinylidene ethylcyano-

BENZOTHIOPHENE



TTNT

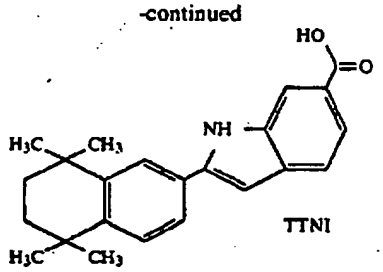
NAPHTHALENE



TTNN

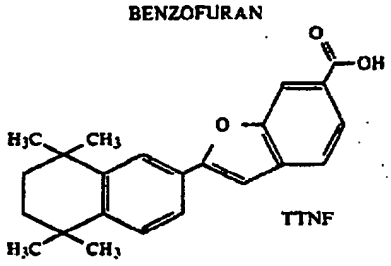
INDOLE

-continued

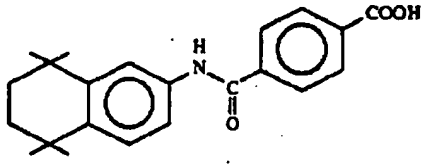


TTNI

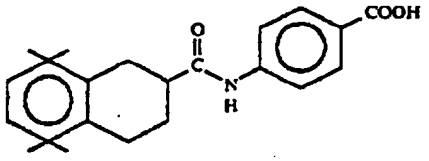
BENZOFURAN



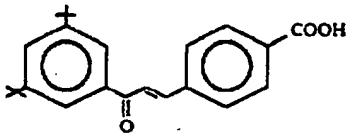
TTNF



Am-80



Am-580



Ch-55

Also included within the foregoing compounds are any halogenated compounds or ether, amide, modified rings, dehydro, dihydro, isomer or analog forms of said compounds.

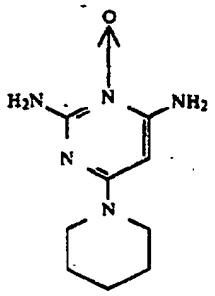
The retinoid compounds useful in the present invention are believed to have the common characteristic of binding to the retinoid cell receptors and thereby stimulating the hair follicle cell proliferation.

Retinoids have been defined narrowly as comprising simply Vitamin A (retinol) and its derivatives such as Vitamin A aldehyde (retinal), Vitamin A acid (retinoic acid), comprising the so-called natural retinoids. Retinol and its esters have been used previously in hair preparations to prevent hair loss, but not to increase or stimulate hair growth in cases of alopecias.

Subsequent research has resulted in a much larger class of chemical compounds that are termed retinoids due to their biological similarity to Vitamin A and its derivatives. Compounds useful in the present invention include natural forms of Vitamin A, Vitamin A acid and its isomers, Vitamin A aldehyde and/or synthetic analogs of Vitamin A acid which possess the biological activity of Vitamin A acid in the hair follicle. Accordingly, as used herein for purposes of the present invention, the term "retinoid" will be understood to include any compound which fits the foregoing chemical and/or biological definitions.

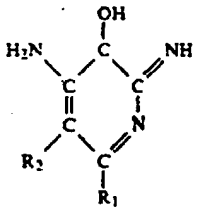
That is, the definition of a retinoid intended in this invention is a substance that can elicit a specific biological response by binding to and activating a specific receptor or set of receptors for retinoids. Therefore, any Vitamin A type compound, whether defined by the classic description of a particular subset of diterpenoid, polyene substances or a new type of synthetic ligand (neither diterpenoid nor polyene) which can have a better molecular fit to the retinoid receptors (cytosolic retinoic acid binding proteins), should be considered in this definition. The biological response of the target cells for retinoids should be defined as any compound (retinoid) which is capable of stimulating the hair follicle cells to differentiate or to turnover more rapidly. This covers compounds traditionally related to retinoids and it also covers compounds which are not diterpenoid types. The ring, the side chain, the terminal group or all of these can be altered. This definition would include even newer retinoids which do not fit the older Vitamin A-type concept but which can be shown to bind to the retinoid receptor proteins specific for retinoic acid (CRABP) within cells of the follicular epithelium. Examples of such newer retinoids include, inter alia, TTNT, TTNN, TTNI, TTNF, Am-80, Am-580 and Ch-55, which are shown above.

Minoxidil (2,4-diamino-6-piperidinopyrimidine-3-oxide) is represented by the following formula:

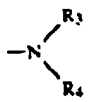


In addition to minoxidil, its active derivatives and analogs can also be used. These active derivatives and analogs are described, for example, in U.S. Pat. Nos. 5,910,928; 3,637,697; 3,461,461; 4,139,619; and 4,596,812, the descriptions of which are fully incorporated herein by reference.

Among the active derivatives and analogs of minoxidil described in these patents are compounds of the formula:



where R_1 is a moiety selected from the group consisting of moieties of the formula



wherein R_3 and R_4 are selected from the group consisting of hydrogen, lower alkyl, lower alkenyl, lower arylalkyl, and lower cycloalkyl, and taken together R_3 and R_4 may be a heterocyclic moiety selected from the group consisting of aziridinyl, acetidinyl, pyrrolidinyl, piperidino, hexahydroazepinyl, heptamethylenimino, octamethylenimino, morpholino, and 4-lower alkylpiperazinyl, each of said heterocyclic moieties having attached as substituents on the carbon atoms 0–3 lower alkyl groups, hydroxy or akloxy, and wherein R_2 is selected from the group consisting of hydrogen, lower alkyl, lower alkenyl, lower alkoxyalkyl, lower cycloalkyl, lower aryl, lower aralkyl, lower alkaryl, lower alkaralkyl, lower alkoxyaralkyl, and lower haloaralkyl, and the pharmacologically acceptable acid addition salts thereof.

See also *J. Heterocyclic Chem.*, 15:1529 (1978) by John M. McCall, et al., the disclosure of which is additionally incorporated herein by reference.

Included as minoxidil analogs are those described in the following U.S. Pat. Nos.: 4,287,338; 4,220,772; 3,464,987; 4,316,901; 3,270,015; 3,270,014; 3,382,248; 3,461,461; 4,080,500; and 3,973,016, the disclosures of which are incorporated herein by reference. Other suitable minoxidil-type compounds include minoxidil glucuronides disclosed in published European application 0242967A1 and the substituted pyrimidine compounds disclosed in my published PCT patent applications WO86/00616 and WO/8504577.

A major problem in influencing hair growth is obtaining good percutaneous absorption of the active compounds. The retinoid compounds described herein cause excellent percutaneous absorption of themselves and other compounds used in combination therewith, and are very active on the keratinizing cells of the skin, including the hair follicles.

Accurate measurement of hair growth to substantiate the results of the testing is often a problem. A microcapillary method which gives excellent results and can be used to measure the rate of hair growth was devised by M. Saitoh, et al., *Advances in Biology of the Skin*, vol. 6, p. 467 (1968) and utilizes microcapillary tubes which are graduated using 0.2 mm graduations. A less time-consuming magnification method which also yields good results involves shaving off of the hairs for examination and measurement.

The pharmaceutical, cosmetic or veterinary preparations of the present invention can be prepared by conventional techniques for the preparation of lotions, creams, conditioners or shampoos for the scalp or veterinary preparations for pelts. Though not as preferred, included also are preparations which can be administered orally and compounds which can be added to animal foods.

In addition to the active combinations of retinoids and minoxidil-type compounds of this invention, the various preparations can contain any conventional pharmaceutically acceptable or cosmetically acceptable inert or pharmacodynamically active additives or carriers. For example, the lotions may be prepared using various forms of alcohols or other solubilizers such as glycols or esters. The conditioners may contain the normally acceptable, comm[illegible]ced pounds such as cetyl alcohol, c[illegible] ins, hydrolyzed animal protein, [illegible] amodimethicone, paraffin, mineral oil, sil[illegible]

The topical compounds may also contain adjunctive compounds, such as oils, including essential fatty acids; vitamins or their derivatives; hormones (natural or synthetic), including progesterones, estrogens including estradiols, thyroids, and polypeptide hormones; and antiandrogens, including but not limited to cyproterone acetate, cyoctol, secosteroids, flutamide or spironolactone, and particularly nonsteroidal antiandrogens such as the decahydro-7H-benz(E)-inden-7-ones described in U.S. Pat. No. 4,466,971. Androgens are known to cause alopecia in genetically programmed individuals, and antiandrogens prevent the effect of the androgen on the nucleus of the hair follicle cell. Therefore, any substance which can prevent the androgen from acting on the nucleus of the cell is considered an antiandrogen.

Examples of the active-type Vitamin D_3 which can be used in combination with the retinoids of this invention include the following types which are not meant to be limiting: 1-hydroxycholecalciferol; 1,25-dihydroxycholecalciferol (commercially available as ROCALTROL); and 1,24-dihydroxycholecalciferol. Vitamin D3 is generally administered at a rate of about 0.001 to 0.3 μg/gm. Vitamin D_3 type compounds have recently been shown to regulate cell differentiation and to promote the differentiation of the keratinocyte. Vitamin D compounds are also important in calcium regulation. These compounds may assist in the conversion of vellus to terminal hairs.

The topically applied lotions, creams, conditioners, or other formulations containing the retinoid will vary according to the standard art with regard to the amounts of other hydrophilic and hydrophobic ingredients, including emulsifiers, so that either an oily, semi-oily or oil-free product may be obtained. The shampoos may contain any of the conventionally used detergents or soaps and any other compounds used by those familiar with the art. Oil-based shampoos are included in these formulations.

The oral preparations may be tablets, liquids, capsules, etc. The pharmaceutically acceptable substances commonly used as preservatives, stabilizers, moisture retainers, emulsifiers, etc., can be present in these preparations. Conventionally acceptable antioxidants such as tocopherols, N-methyl 2-tocopheramine, butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT), can be incorporated also in the preparations described herein.

Retinoids and minoxidil are administered in effective amounts which vary with the route of administration and the requirements of the subjects. The topical treatments may consist of lotions, creams, conditioners, shampoos, oil treatments, etc., with about 0.001 to 2% by weight of all-trans retinoic acid or derivatives, or other retinoids, as the preferred dosages in the described compositions and with dosages of about 0.01% to 30% minoxidil in suitable vehicles for topical use. Arotinoids may be effectively used at doses as low as 0.00001% by weight or even lower. Oral dosages for minoxidil should not exceed 10 mg/day total dose, and for retinoic acid 1 mg/kg body weight/day is a maximal dose which will eventually cause toxicity and with chronic treatment will probably cause the hair to fall

enhance!

...dat. The ... mg/kg body weight should be a ... able dose.

... examine the specific action of the retinoic acid and minoxidil in increasing the rate of hair growth, several types of experiments were performed. The microcapillary method was used in each case to measure the rate of hair growth. Other methods of dye staining and hair growth measurements were also undertaken. In addition, the method of Ebling, et al., *Journal of Investigative Dermatology*, November 1981, was used to study the conversion of vellus to terminal hairs by microscopy.

The effectiveness of the active ingredients of this invention for increasing the rate of or stimulating hair growth will now be illustrated by the following examples. These examples, however, are merely representative and should not be construed so as to limit the scope of the invention.

EXAMPLE I

A topical lotion containing 0.1 percent by weight of all-trans retinoic acid and 3% by weight minoxidil was included in the preparation to be tested. As the vehicle, 5 weight percent propylene glycol, 1 mg per 100 ml butylated hydroxytoluene (BHT), and 95 weight percent ethanol were mixed in a beaker for several minutes at ambient conditions to obtain a homogeneous preparation in which the retinoid was dissolved. This lotion was labelled A and was the active drug preparation. A similar lotion was prepared by the foregoing procedure containing all the aforementioned ingredients, but omitting the retinoid and minoxidil. This preparation was labelled B and was the placebo lotion.

Volunteer subjects had a 3 to 4 cm diameter area of scalp hair bleached at the scalp end. The subjects were asked to apply the (placebo) lotion B, 2 times a day, to the scalp for varying periods of time from 10 to 30 days. The rate of hair growth in each individual was determined using measurements taken with either microcapillary measuring equipment or by magnification measurements. The rate of new hair growth from the scalp end to the bleached area was recorded every three to six days. The data is expressed as control rate of hair growth in mm of growth per day.

At the end of the placebo treatment, anagen/telogen ratios were determined by the following standard method of Orentreich, N. and Berger, R. A. "Selenium disulfide shampoo", *Arch. Derm.* 90:76–80 (1964): Hair plucking Was done from the areas treated before and after treatment. A large surgical-needle-holding clamp, with jaws covered with a smooth layer of rubber was used. Twenty to fifty hairs were grasped at one time, approximately 1.0 cm above the scalp surface, and epilated with a single forceful pull. The hair roots and lower portion of the shafts were then cut off into shallow plastic Petri dishes, previously gridded into 1 cm squares, moistened with tap water, and examined and counted by transmitted light with a low-power dissecting microscope. The roots could also be stained to help in the interpretation.

Following the placebo treatment, the subjects were given lotion A (containing the active drug) or lotion B and asked to apply the lotion in the same manner in which they had applied the previous (placebo) lotion. The same procedure was followed for measuring hair growth, namely every three to six days the subject returned for measurements to determine rate of hair growth. At the end of the active drug treatment period, subjects again had anagen/telogen ratios determined. Neither the subjects nor the observers were told which lotion A or B was the active preparation until after the data were analyzed.

Before treatment and at monthly intervals thereafter, a circle 1 inch in diameter was drawn over the balding spot of the vertex with a skin marker and a template. The center of the circle was located by a three-point measurement, using the midpoint between the ears and a fixed distance from the base of the nose. These measurements were recorded at each visit. With the aid of a magnifying lens, the hairs in the 1-inch diameter circle were counted and typed as vellus hairs, indeterminate hairs, or terminal hairs. Nonpigmented short hairs were defined as vellus; pigmented hairs ranging from thin and short to slightly longer and thicker were defined as indeterminate. Hairs of the same color and bore diameter as those in adjacent nonbalding areas were classified as terminal. The count was repeated several times and the average used as the final count. The number of vellus and terminal hairs were compared before, during and at the final visit, and calculated as percent conversions from vellus to terminal.

In Table I are described the results of studies using male and female subjects. The all-trans retinoic acid and minoxidil in lotion form was applied topically or as described in Table I, and hair growth rates were assessed along with conversion of vellus to terminal hair.

TABLE I

Subject Sex	Age	Dosage (ml/day)	Lotion Containing All-Trans Retinoic Acid 0.1% and Minoxidil 3% Form of Dosage	Treatment Time (Months)	Rate of Growth (mm/day) Control (Lotion B)	Treatment (Lotion A)	% Conversion Vellus to Terminal
M	37	10	Topical	2	0.23	0.30	11%
M	62	10	Topical	2	0.21	0.29	22%
M	38	10	Topical	2	0.35	0.42	35%
F	43	10	Topical	2	0.37	0.39	13%
F	38	10	Topical	2	0.31	0.35	18%
F	64	10	Topical	2	0.24	0.29	17%

COMPARATIVE STUDY

A group of twenty normotensive subjects, twenty to sixty-four years of age and clinically diagnosed as suffering from androgenetic alopecia, were entered into a combined study in which twelve subjects received 0.025% topical tretinoin solution with the vehicle as discussed above (95% ethanol, 5% propylene glycol and 1 mg BHT per 100 ml), 36 subjects received a combination of 0.025% tretinoin and 0.5% minoxidil solution, five subjects received the vehicle alone as a pla-

cebo, three subjects received 0.5% minoxidil solution alone, according to the following protocol. Food coloring was added to the placebo and minoxidil solutions to match the color of the retinoic acid.

The subjects were instructed to apply 1 ml of the solution twice daily by dropper to the affected scalp area (a circular area of baldness, 1 inch in diameter). The subjects were advised to wear a cap for protection from the sun or to refrain from excessive sun exposure, and to avoid trauma to the scalp (i.e., vigorous scalp scrubbing or brushing). Blood pressure, serum chemistry tests, complete blood counts, weight, pulse and electrocardiogram were performed before treatment and at repeated intervals for each patient; skin irritation was assessed during each follow-up visit; photographs were taken before and during treatment to evaluate hair growth; and hair counts were performed initially, at monthly intervals, or at follow-up visits.

After analysis of the data, the subjects were placed into one of three designated response groups, with percent increase in number of terminal hairs (defined as thick, pigmented hairs, comparable to those on the subjects' posterior scalp) being the primary criterion for placement. Participants in the "good" response group (Group A) experienced greater than 46% increase in the number of hairs in the target area after treatment; individuals in the "moderate" response group (Group B) had a post-therapy terminal hair increase between 21% and 45%; while participants in the "no response" group (Group C) experienced increases below 20%. The mean amount of time for subject participation was 10, 8 and 9 months, respectively, for Groups A, B and C, and the results are indicated in Table II below.

TABLE II

		Response		
Treatment	No. of Patients	Good (Group A)	Moderate (Group B)	None (Group C)
Placebo	5	0	0	5 (100%)
Minoxidil	3	0	0	3 (100%)
Tretinoin	12	2 (16%)	5 (42%)	5 (42%)
Combination	36	16 (44%)	8 (22%)	12 (33%)

In 56 subjects, 48 of whom were receiving tretinoin or the combination formulation, positive responses were documented in more than half of the subjects, usually within 18 months. The five patients receiving placebo demonstrated no significant hair growth response. Three patients receiving the 0.5% minoxidil solution also showed no meaningful results. Of the 5 men who received tretinoin only, two experienced some hair growth after treatment, although the hairs were mostly of the lanugo (vellus) type.

However, surprisingly, of the patients treated with the combination solution (0.5% minoxidil and 0.025% tretinoin), 66% responded positively, with 44% placed in the good response group and 22% in the moderate response group. These data suggest that there may be a synergism between minoxidil and tretinoin when the substances are combined and used topically. While neither compound alone appears to have profound effects on advanced alopecias, in combination the compounds may be more effective as promoters of new hair growth in individuals with alopecia.

While this study used only 0.5% minoxidil in combination with retinoic acid, other studies report that 2% to 5% minoxidil concentrations cause a cosmetically visible hair regrowth in 30% to 40% of subjects. The above results show that low concentrations of minoxidil (only 1/4 to 1/10 the topical minoxidil concentrations previously reported) are effective when used in combination with tretinoin, suggesting that mixtures of minoxidil and retinoids may be more effective in the treatment of alopecia than is minoxidil alone.

More details of the above study, including photographs of the patients, may be found in Bazzano et al., "Topical Tretinoin for Hair Growth Promotion," *Journal of the American Academy of Dermatology*, 15:4, Pages 880-883 and 889-893 (October 1986).

The following Examples illustrate forms of topical application of compositions of the present invention. The methods of administration may vary by lotion, cream, ointment, pill, supplement to animal food, coating for seeds, etc. These Examples are only meant to be illustrative, and do not limit the mode of administration nor the ingredients which can be admixed to the present invention, nor the amounts which may be used.

FORMULATION EXAMPLE I

Lotion Formulation for the Topical Administration

Ingredients	Weight %
All-trans retinoic acid or 13-cis retinoic acid	0.01 to 0.1
Minoxidil	0.5 to 5.0
Ethanol	q.s. to 100.0
Propylene glycol	5.0 to 50.0
Butylated hydroxytoluene (BHT)	0.1
Distilled water	up to 10.0

FORMULATION EXAMPLE II

Cream Conditioner for Topical Administration

Ingredients	Weight %
All-trans retinoic acid or 13-cis retinoic acid	1.0
Minoxidil	10.0
Distilled water	q.s. to 100.0
Cetrimonium Chloride	5.0
Cetyl alcohol	4.0
Ethanol	4.0
Butylated hydroxytoluene	1.0
Hydrolized animal protein	0.5
Methylparaben, propylparaben	0.1
Stabilizer	0.1

In this example, a higher concentration of active ingredient was used since the conditioner is rinsed out shortly after application.

FORMULATION EXAMPLE III

Hydrophilic Ointment for Topical Administration

All-trans retinoic acid (0.01 to 0.1 gram) and 1-10 grams of minoxidil are dissolved in 100 ml of acetone, and the solution is then admixed with 900 g of USP grade hydrophilic ointment to a uniform consistency; one gram of butylated hydroxytoluene is added. A water washable cream ointment is thus prepared.

FORMULATION EXAMPLE IV

Tablets for Oral Administration

Ingredients	Amounts
Minoxidil	10 mg.
All-trans retinoic acid or	25 mg.

-continued

Ingredients	Amounts
13-cis retinoic acid	
Lactose	52 mg.
Cornstarch	20 mg.
Microcystalline cellulose	40 mg.
Talc	2.5 mg.
Magnesium stearate	0.5 mg.

The active ingredients are mixed with lactose and granulated using a cornstarch paste. The remainder of the above adjuvants are then admixed therein, and the mass is tableted. The tablets are then coated with a water-soluble or water-swellable lacquer. Liquids, syrups or other formulations can be made consistent with pharmaceutical art.

The retinoid/minoxidil combinations of the invention may also be used in veterinary preparations or feeds to increase the rate of growth of fur (pelt) in certain fur bearing animals and to retard shedding and molting.

In fur bearing animals, the rate of fur growth, length of hair, thickness of hair and molting season are controlled by many factors including season, light (wavelength) periodicity, temperature, hormonal factors and nutrition. Controlling all of these variables is impossible. However, animals were selected and areas over the hind quarters were shaved in 2 inch diameter circular areas. In some of the animals the areas were treated topically with all-trans retinoic acid, and in other animals the retinoid was administered orally in animal chow. Some of the animals served as their own controls, using treated and non-treated areas.

In fur bearing animals, the guard hairs and the pile hairs differ in thickness, length and growth rate. In the rabbits studied, the guard hairs averaged 34 mm and the pile hairs 30 mm in length. The effect of topical application of all-trans retinoic acid was to increase the rate of new hair growth. An effect on the non-shaved fur bearing areas treated with topical all-trans retinoic acid in lotion form, was a decrease in the shedding or molting of fur. The mean rate of hair (fur) growth from treated shaved areas was 0.3 mm per day for 3 rabbits (mean) while in non-treatment shaved areas it averaged 0.2 mm per day (mean of 3 rabbits).

The effect could also be demonstrated in domestic cats and dogs; the same type of experimental procedures were used. The most striking effect in long haired dogs and cats was the retardation of molting or hair shedding. Long haired dogs and cats tended to retain more hair in the anagen phase and there was approximately 50% less shedding during the treatment periods. Both methods of administration were satisfactory. Either topical lotion or cream treatment or systemic treatment by inclusion in animal chow was satisfactory. The daily dosage for animals was 20 mg per kilogram animal chow or 10 to 15 mg applied topically.

Commerically important fur bearing animals were also used for experimentation. Two male minks were closely clipped over the back hind quarters. The animals were treated on one hind quarter and the other was used as the control. The microcapillary method for measuring hair growth was used for these studies. The animals were treated by two different methods. The animals were either fed the retinoid in their chow or they were administered the retinoid topically. The daily dose was 20 mg per kg animal chow or 5 mg per day applied topically. The results of these experiments showed that the rate of growth of new pelt was increased approximately 30% by the retinoid treatment.

Experiments using birds (canaries and parakeets) showed that inclusion of the all-trans retinoic acid or the ethyl ester of all-trans retinoic acid in bird food at a dosage of 30 mg per kilogram bird seed retarded the molting process.

The present invention may be embodied in other specific forms without departing from the spirit or the central attributes thereof and, accordingly, reference should be made to the appended claims, rather than to the foregoing specification as indicating the scope of the invention.

I claim:

1. A composition for treating alopecia comprising a retinoid and a minoxidil compound, said compound being present in an amount of about 0.01 to 30 percent by weight and said retinoid being present in an amount of about 0.001 to 2 percent by weight in said composition.

2. A composition according to claim 1 wherein said retinoid is Vitamin A acid.

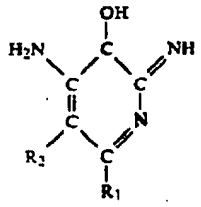
3. A composition according to claim 1 wherein said compound is minoxidil (2,4-diamino-6-piperidinopyrimidine-3-oxide).

4. A composition according to claim 3 wherein said retinoid is Vitamin A acid.

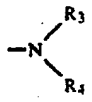
5. A composition according to claim 1 wherein said composition also includes a pharmaceutically effective vehicle for said compound and said retinoid.

6. A composition according to claim 5 wherein said vehicle comprises ethanol and propylene glycol.

7. A composition according to claim 1 wherein said compound has the formula:



wherein R_1 is a moiety selected from the group consisting of moieties of the formula



wherein R_3 and R_4 are selected from the group consisting of hydrogen, lower alkyl, lower alkenyl, lower aralkyl, and lower cycloalkyl, and taken together R_3 and R_4, may be a heterocyclic moiety selected from the group consisting of aziridinyl, azetidinyl, pyrrolidinyl, piperidino, hexahydroazepinyl, heptamethylenimino, octamethylenimino, morpholino, and 4-lower alkylpiperazinyl, each of said heterocyclic moieties having attached as substituents on the carbon atoms 0-3 lower alkyl groups, hydroxy or alkoxy, and wherein R_2 is selected from the group consisting of hydrogen, lower alkyl, lower alkenyl, lower alkoxyalkyl, lower cycloalkyl, lower aryl, lower aralkyl, lower alkaryl, lower alkaralkyl, lower alkoxyaralkyl, and lower haloaralkyl, and the pharmacologically acceptable acid addition

salts thereof, said retinoid and said compound being applied in amounts which are effective to increase the rate of hair growth.

13. A method for treating alopecia caused by a shortening of the anagen (growing) phase of the hair cycle, which comprises topically applying to the scalp a minoxidil compound and a retinoid, said compound and said retinoid being applied in amounts which are effective to stimulate hair follicles of said scalp to produce hair growth therefrom.

14. A method for treating alopecia caused by a shortening of the anagen (growing) phase of the hair cycle, which comprises topically applying to the scalp a minoxidil compound and a retinoid, said compound and said retinoid being applied in amounts which are effective to prolong the anagen phase of the hair cycle.

15. A method for treating alopecia caused by a shortening of the anagen (growing) phase of the hair cycle, which comprises topically applying to the scalp a minoxidil compound and a retinoid, said compound and said retinoid being applied in amounts which are effective to convert vellus hair to growth as terminal hair.

16. A method of retarding shedding in fur bearing animals comprising topical administration to the animal of an effective amount of a retinoid and a minoxidil compound.

17. A method of retarding molting in birds comprising topical administration to the bird of an effective amount of a retinoid and a minoxidil compound.

18. In a method for treating alopecia caused by a shortening of the anagen (growing) phase of the hair cycle which comprises topically applying to the scalp an effective amount of a minoxidil compound, the improvement consisting of said topical application including a retinoid in an amount which is effective to increase the rate of hair growth.

19. A method for treating alopecia caused by a shortening of the anagen (growing) phase of the hair cycle, which comprises topically applying to the scalp a minoxidil compound and a retinoid, said compound and said retinoid being applied in amounts which are effective to increase the rate of hair growth.

20. A method according to claim 19 wherein said retinoid is Vitamin A acid.

21. A method according to claim 19 wherein said compound is minoxidil (2,4-diamino-6-piperidinopyrimidine-3-oxide).

22. A method according to claim 21 wherein said retinoid is Vitamin A acid.

23. A method according to claim 19 wherein said compound and said retinoid are applied in combination with a pharmaceutically acceptable vehicle.

24. A method according to claim 23 wherein said vehicle comprises a mixture of ethanol and propylene glycol.

25. The method of claim 19 wherein said retinoid is selected from the group consisting of all-trans retinoic acid, all-trans retinaldehyde, all-trans retinoyl acetate, and pharmaceutically acceptable salts, ethers, amides or esters thereof.

26. The method of claim 19 wherein the retinoid is an isomer of Vitamin A acid selected from the group consisting of 13-cis; 9,13-dicis; 9-cis; 11-cis; or 7,8-dehydro retinoic acid; Vitamin A_2 acid; α-Vitamin A acid; γ-Vitamin A acid; 5,6-epoxy Vitamin A acid; dehydrovitamin A acid; anhydro Vitamin A acid; and pharmaceutically acceptable salts of said isomer.

27. The method of claim 23 wherein said combination further comprises Vitamin D_3 or a Vitamin D_3 derivative selected from the group consisting of 1-hydroxycholecalciferol; 1,25-dihydroxycholecalciferol; and 1,24-dihydroxycholecalciferol.

28. The method of claim 23 wherein said combination further comprises a hormone selected from the group consisting of estrogens and progesterones.

29. The method of claim 23 wherein said combination further comprises an antiandrogen selected from the group consisting of cyproterone acetate, spironolactone, secosteroids, flutamides, cyoctol, and decahydro-7H-benz(E)-inden-7-ones.

30. A method for treating alopecia caused by a shortening of the anagen phase of the hair cycle which comprises topically applying to the scalp minoxidil and all-trans retinoic acid in amounts which are effective to increase the rate of hair growth.

* * * * *

United States Patent [19]

Gibson

[11] **Patent Number: 5,015,470**

[45] **Date of Patent: May 14, 1991**

[54] **COSMETIC COMPOSITION**

[76] Inventor: **Walter T. Gibson**, 8 Braid Court, Wellingborough, Northants NN8 3PF, England

[21] Appl. No.: **134,422**

[22] Filed: **Dec. 17, 1987**

[30] **Foreign Application Priority Data**

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[51] **Int. Cl.**[5] **A61K 7/06**

[52] **U.S. Cl.** **424/70**; 514/2; 424/603; 424/660; 424/673; 424/663; 424/709; 424/711; 435/200

[58] **Field of Search** 424/70, 603, 660, 673, 424/663, 709, 711; 514/880, 881; 435/200

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Primary Examiner—Ronald W. Griffin

Attorney, Agent, or Firm—Melvin H. Kurtz

[57] **ABSTRACT**

A composition suitable for topical application to mammalian skin or hair for inducing, maintaining or increasing hair growth comprises:

(i) a first chemical inhibitor chosen from proteoglycanase inhibitors, glycosaminoglycanase inhibitors, glycosaminoglycan chain cellular uptake inhibitors or mixtures thereof; and

(ii) a cosmetically acceptable vehicle for the chemical inhibitor;

provided that when the first chemical inhibitor is a weak inhibitor, such that a 1 mM aqueous solution of the inhibitor reduces proteoglycanase activity, glycosaminoglycanase activity or cellular uptake of glycosaminoglycan chains, by from 5 to 50%, in accordance with at least one of the assay tests as herein described, then there is also present in the composition a second chemical inhibitor and/or an activity enhancer. When minoxidil is the sole chemical inhibitor, then the activity enhancer is a penetration enhancer chosen from a limited number of materials, including certain esters and cationic polymers.

The total amount of chemical inhibitor present in the composition is sufficient to increase hair growth in the rat, when said composition is applied topically thereto, by at least 10% more than that obtainable using a control composition from which the said inhibitors have been omitted.

31 Claims, No Drawings

COSMETIC COMPOSITION

FIELD OF THE INVENTION

The invention relates to cosmetic and pharmaceutical compositions for topical application to mammalian skin or hair, containing an enzyme inhibitor which is capable of promoting hair growth, especially terminal hair growth on the human scalp.

BACKGROUND

The Hair Growth Cycle

It should be explained that in most mammals, hair does not grow continuously, but undergoes a cycle of activity involving alternate periods of growth and rest. The hair growth cycle can be divided into three main stages, namely:

(i) the growth phase known as anagen, during which the hair follicle penetrates deep into the dermis with the cells of the bulb dividing rapidly and differentiating to form the hair,

(ii) the transitional stage known as catagen, which is heralded by the cessation of mitosis, and during which the follicle regresses upwards through the dermis and hair growth ceases,

(iii) the resting stage known as telogen, in which the regressed follicle contains a small secondary germ with an underlying ball of tightly packed dermal papilla cells.

The initiation of a new anagen phase is revealed by rapid proliferation in the germ, expansion of the dermal papilla and elaboration of basement membrane components. The hair cycle is then repeated many times until, as a consequence of the onset of male pattern baldness, most of the hair follicles spend an increasing proportion of their time in the telogen stage, and the hairs produced become finer, shorter, and less visible; this is known as terminal to vellus transformation.

PRIOR ART

Alleged Baldness Cures

Although there have been many claims in the scientific literature to the promotion or maintenance of hair growth by the topical application of hair tonics and the like, with the possible exception of minoxidil, none has been shown to be sufficiently free from disadvantageous clinical side effects, whether administered topically, orally or systemically, to warrant commercial exploitation as an ethical pharmaceutical, proprietary medicine, or as a cosmetic product. Possibly, the only means which has met with partial success for growing hair on the bald or balding human head is by transplantation of hair to the bald areas. This is, however, an extremely painful operation and is not always successful. Furthermore, it is immediately apparent to the casual observer that the subject has received a hair transplant and it may take many months or even years before hair regrowth, following this operation, assumes an appearance which resembles that of the original naturally growing hair.

Among the many hair regrowth studies that have been reported in the literature, there is included the work of Bazzano as described in PCT International Publication No. WO 85/04577. This publication describes a composition which is useful for increasing the rates of hair growth on mammalian skin, prolonging the anagen phase of the hair growth cycle and for treating various types of alopecias. The composition in question comprises a pyrimidine carbamate.

It has also been reported in US patent no. 4 139 619 to Chidsey assigned to the Upjohn Company, that a topical composition comprising minoxidil as the free base or acid addition salt thereof, or certain specified related iminopyrimidines, is useful in stimulating the conversion of vellus hair to growth as terminal hair, as well as increasing the rate of growth of terminal hair.

In spite of the apparent stimulation of hair growth or regrowth reported independently by Bazzano and Chidsey, following topical application of minoxidil or related compounds, there is general concern that systemic side-effects can result, particularly following topical application of minoxidil. Thus it is generally recognised in the medical literature that the side effects of orally administered minoxidil are very serious, and include fluid retention, tachycardia, dyspnea, gynecomastia, fatigue, nausea and cardiotoxicity. There is also evidence that certain side effects have been experienced following topical application of minoxidil.

In addition to the alleged benefits of employing the pyrimidine carbamates of Bazzano or minoxidil of Upjohn, many other hair regrowth studies have been reported in the literature. In particular, the work of Meyer et al (1961) in the Proceedings of the Society of Experimental and Biological Medicine, 108, 59–61, is worthy of mention. Meyer and his co-workers repeatedly injected acid mucopolysaccharides into the skin of shaved rabbits and reported observing the initiation of the hair growth cycle with stimulation of hair growth which in some instances appeared to be thicker than usual. They found that heparan sulphate was particularly active, while dermatan sulphate and chondroitin-6-sulphate were also active in this respect, but to a lesser extent.

It has also been reported by Frajdenrajch in EP-A-O 035 919 to include chondroitin sulphate in a hair composition in order to prevent loss and encourage growth of the hair.

Also, Shansho Seigaku in JA-59/186911 describes a shampoo containing a mucopolysaccharide such as chondroitin sulphate.

There are also other references, mainly of Japanese origin, which claim the use of chondroitin sulphate in preparations for topical application to human skin, particularly as hair tonics.

Kohler in DE OLS 24 38 534 reports that D-glucuronic acid and glucuronic acid γ-lactone (also known as glucurono-6,3-lactone) can be applied externally to the skin, together with vitamin C and water, ethanol or aqueous ethanol as a vehicle, as a scalp care agent. In a particular experiment, Kohler reports regrowth of hair following daily application for six months of a 1% solution of D-glucuronic acid.

Kohler et al in DE OLS 26 19 100 also claims the use of glucuronic acid or glucuronic acid γ-lactone as inhibitors in agents for inhibiting the activity of γ-glucuronidase, particularly in combination with vitamin B_{12}. Whereas Kohler et al are concerned with γ-blucuronidase as found in unusually high concentrations in healing wounds and cancer tissues, they do state that the agents also have a beneficial effect on the loss of hair.

In experiments to be described later in this specification, we have found that both glucuronic acid and glucurono-6,3-lactone are weak inhibitors of γ-glucuronidase activity and require the presence of a second inhibitor and/or a special activity enhancer, as

hereinafter defined, to provide significant hair growth or regrowth. The weak inhibition by glucuronic acid in this respect has also been confirmed by Levvy and Snaith (1972) in "Advances in Enzymology" 36 where, at page 156 they state that:

"Both β-glucuronidase and α-glucuronidase are feebly inhibited by glucuronic acid . . . "

BACKGROUND OF THE INVENTION

The above review of the most relevant references concerning the alleged promotion of hair growth following topical or systemic application of specified molecules, has prompted the study in greater detail, of the biological and biochemical mechanisms involved in the control of the hair growth cycle. The reported role of the dermal papilla which is situated at the base of the hair follicle, and the closely related cells of the connective tissue sheath which surrounds the hair follicle are alleged to be of key importance in governing the cyclic behaviour of hair follicles. This has been shown, for example, directly by Oliver R F (1970) J Embryol Exp Morphol., 23, 219–236, and the changes in the dermal papilla during the hair cycle are consistent with these observations. At the end of anagen, there is a sudden loss of fibronectin [Couchman J R and Gibson W T, (1985) Dev Biol , 108, 290–298]and metachromatic (glycosaminoglycan) staining [Montagna W et al, (1952) Q J Microsc Sci., 93, 241–245]from the connective tissue matrix of the dermal papilla which then undergoes condensation.

Conversely, expansion and elaboration of new matrix is associated with the onset of anagen. A direct role of matrix components in stimulating hair growth was suggested by the work of Meyer et al (1961), [supra].

It is accordingly apparent that glycosaminoglycan breakdown is an important early change in catagen, and since there is already evidence for a link between the presence of intact glycosaminoglycans and hair growth, we have suggested that prevention of proteoglycan and glycosaminoglycan breakdown may lead to earlier onset and/or prolongation of anagen. This would effectively retard hair loss and reverse baldness.

When considering the breakdown of glycosaminoglycans, it must be remembered that these are complex polysaccharides built up from alternating hexosamine and uronic acid units. Modification of these units by N-and/or and/or O-sulphation, and by N-acetylation provides further scope for diversity, which necessitates the concerted, sequential action of a range of enzymes for complete degradation to occur. Furthermore, glycosaminoglycans normally exist in the form of a proteoglycan, in which glycosaminoglycan chains are attached to a protein core. Degradation can therefore occur by the action of proteolytic enzymes ("proteoglycanases") on the protein core, causing release of intact glycosaminoglycan chains which are taken up by cells or removed in the circulation, or by the action of endoglycosidases, exoglycosidases and sulphatases ("glycosaminoglycanases") which cleave the glycosaminoglycan molecule at specific sites. It follows that glycosaminoglycan breakdown may be prevented in a number of ways, viz by inhibiting proteoglycanase activity, by blocking cellular uptake of intact glycosaminoglycan chains, and/or by inhibiting glycosaminoglycanase activity.

We have now identified chemical inhibitors of key enzymes and other cellular events involved respectively in the breakdown of proteoglycan or glycosaminoglycan chains, and in the blocking of cellular uptake of intact glycosaminoglycan chains.

It should be explained by "chemical inhibitor" is meant a substance that is physiologically suitable and safe for topical application to human skin, and which is capable of inhibiting proteolytic breakdown of the proteoglycans or inhibiting glycosidase or sulphatase enzymes involved in the breakdown or modification of glycosaminoglycan side chains by direct, enzyme inhibition or by protecting the substrate so that the enzyme does not recognise it, or inhibiting cellular events involved in the recognition and uptake of glycosaminoglycans.

We have accordingly found that these inhibitors will indeed stimulate hair growth as predicted on the basis of the theory outlined above.

DEFINITION OF THE INVENTION

Accordingly, the invention provides a composition suitable for topical application to mammalian skin or hair for inducing, maintaining or increasing hair growth which comprises:

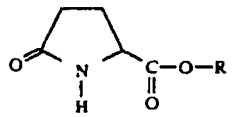
(i) a first chemical inhibitor chosen from proteoglycanase inhibitors, glycosaminoglycanase inhibitors, glycosamincglycan chain cellular uptake inhibitors or mixtures thereof; and

(ii) a cosmetically acceptable vehicle for the chemical inhibitor;

provided that when the first chemical inhibitor is a weak inhibitor, such that a 1mM aqueous solution of the inhibitor reduces proteoglycanase activity, glycosaminoglycanase activity or cellular uptake of glycosaminoglycan chains, by from 5 to 50%, in accordance with at least one of the assay tests as herein described, then there is also present in the composition a second chemical inhibitor and/or an activity enhancer; provided also that when minoxidil is the sole chemical inhibitor then the activity enhancer is a penetration enhancer chosen from:

Dioctyl adipate
Dicapryl adipate
Diisopropyl adipate
Diisopropyl sebacate
Dibutyl sebacate
Diethyl sebacate
Dimethyl sebacate
Dioctyl sebacate
Dibutyl suberate
Dioctyl azelate
Debenzyl sebacate
Dibutyl phthalate
Dibutyl azelate
Ethyl myristate
Dimethyl azelate
Butyl myristate
Dibutyl succinate
Didecyl phthalate
Decyl oleate
Ethyl caproate
Ethyl salicylate
Isopropyl palmitate
Ethyl laurate
2-ethyl-hexyl pelargonate
Isopropyl isostearate
Butyl laurate

Benzyl benzoate
Butyl benzoate
Hexyl laurate
L- Ethyl caprate
Ethyl caprylate
Butyl stearate
Benzyl salicylate
2-hydroxypropanoic acid
2-hyroxyoctanoic acid,
esters of pyroglutamic acid having the structure:



(1)

where R is C_1 to C_{30} alkyl, or

and where R' and R" are the same or different and are each represented by H or the grouping:

$$(CH_3)_u\ (CH_2OH)_v\ (CH_2)_w\ (CH_3CH_2)_x\ (CH{=}CH)_z \quad (2)$$

where
u is zero or 1
v is zero, or the integer 1 or 2,
w is zero, or an integer of from 1 to 21
x is zero, or an integer of from 1 to 4,
y is zero, or the integer 1 or 2,
z is zero, or an integer of from 1 to 22, and
u+v+w+x+y+z is an integer of from 1 to 22;
provided that when the subgrouping (CH=CH) is present, then the total number of carbon atoms in said grouping is from 10 to 22; and/or
a cationic polymer chosen from:
Guar Hydroxypropyltrimonium chloride
Quaternium-19
Quaternium-23
Quaternium-40
Quaternium-57
Poly(dipropyldiallylammonium chloride)
Poly(methyl-β-propaniodiallylammonium chloride)
Poly(diallylpiperidinium chloride)
Poly(vinyl pyrinium chloride)
Quaternised poly (vinyl alcohol) and
Quaternised poly-(dimethylaminoethylmethacrylate);
the total amount of chemical inhibitor present in the composition being sufficient to increase hair growth in the rat, when said composition is applied topically thereto, by at least 10% more than that obtainable using a control composition from which the said inhibitors have been omitted.

DISCLOSURE OF THE INVENTION

The Chemical Inhibitor

As has already been stated, a "chemical inhibitor" is a substance which is not only physiologically suitable and safe for topical application to skin, but which is capable of inhibiting in some way proteoglycanase activity, and/or glycosaminoglycanase activity and/or cellular uptake of glycosaminoglycan chains.

It is preferred that the chemical inhibitor is one which is significantly effective in at least one of these respects, that is, it is a strong inhibitor which is normally capable at a concentration of 1mM of reducing said activity or cellular uptake by more than 50%. For less effective inhibitors, ie., weak inhibitors, which are only capable, at this concentration, of reducing said activity or cellular uptake by from 5 to 50%, then it is necessary to include in the composition according to the invention a second chemical inhibitor and/or an activity enhancer.

In view of the complexity of the proteoglycan and glycosaminoglycan chain which can be degraded in different ways with a variety of enzymes, it is necessary to screen a potential chemical inhibitor in at least one of several different assay systems. Suitable assays which can be employed for endoglycosidases, exoglycosidases, sulphatases, sulphamatases are described in "Lysosomes—A Laboratory Handbook", Second Edition (1977) edited by J. T. Dingle. Proteoglycanase inhibitors may be conveniently assayed by the method described by Nagase & Woessner (1980) in Analyst. Biochem. 107, 385. Cellular uptake inhibition may be assessed by using radioactively labelled glycosaminoglycans according to the method described by Eskild W, et al., (1986) in Int. J. Biochem. 18, 647.

Suitable assay methods for each of the relevant enzymes and their inhibition by chemical inhibitors will be described and illustrated later in this specification.

The Proteoglycanase Inhibitors

According to one embodiment of the invention, the composition comprises a direct proteoglycanase inhibitor, that is a substance which will suppress the activity of proteinase enzymes present in or in the region of the dermal papilla, and/or the connective tissue sheath of the hair follicle.

An example of a direct proteoglycanase inhibitor of this type is 1,10-phenanthroline, also identified by Galloway et al, (1983) in Biochem. J. 209, 741-742, as a bone proteoglycanas inhibitor.

Further examples of direct proteoglycanase inhibitors include various thiol, carboxyalkyl and hydroxamic peptide inhibitors, such as those described by Caputo et al., (1987) in Biochemical Pharmacology 36, 995-1002 as effective inhibitors of the action of a metalloproteinase on proteoglycan core protein. These inhibitors include:
Thiols, such as
AcetylPhe-LeuSH
AcetylSer-LeuSH
AcetylTrp-LeuSH
AcetylPhe-Phe-LeuSH
$HSCH_2CH$(i-Butyl)$COPheNH_2$
$HSCH_2CH$(i-Butyl)COLeu-$PheNH_2$
AcetylTrp-IleSH
AcetylPhe-IleSH
Carboxylic acids, such as
$HOOCCH$(i-Butyl)Leu-Leu-$LeuOCH_3$
$HOOCCH$(i-Butyl)Leu-Leu-$AlaNH_2$
$HOOCCH$(i-Butyl)Leu-Leu-$PheNH_2$
$HOOCCH$(i-Butyl)Leu-Leu-Leu-$AlaNH_2$
Hydroxamic acids, such as
$HONHCOCH_2CH$(n-Pentyl)COLeu-$PheNH_2$
$HONHCOCH_2CH$(n-Pentyl)COLeu-AlaNH
$HONHCOCH_2CH$(i-Butyl)COLeu-$PheNH_2$
HONHCOCH CH(n-Pentyl)COVal-$AlaNH_2$

According to a further embodiment of the invention, the composition can comprise an indirect proteoglycanase inhibitor, that is a substance which modifies the

proteoglycan substrate so that the proteoglycanase does not recognise it. An example of an indirect proteoglycanase inhibitor of this type is the class of compounds defined as cationic oligomers.

According to this embodiment of the invention, there is provided a composition which comprises one or more oligomeric molecules containing one or more cationic groups which will bind to negatively charged anionic proteoglycan molecules and protect them from enzymic attack. Preferred cationic oligomers may be chosen from those which are rich in arginine and/or lysine, containing up to 20, preferably 5 to 10 amino acids in sequences similar to or the same as those found in naturally occurring basic proteins such as protamines and histones.

Specific examples of cationic oligomers are:
Arg-Arg-Arg,
Cys-Arg-Arg-Arg-Lys-Arg-Arg,
Pro-Arg-Arg-Arg-Arg, and
Arg-Pro-Val-Arg-Arg-Arg-Arg-Arg-Pro-Val.

The Glycosaminoglycanase Inhibitors

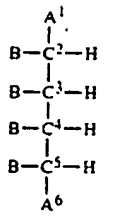
According to a further embodiment of the invention, the composition comprises a glycosaminoglycanase inhibitor chosen from endoglycosidase inhibitors, exoglycosidase inhibitors, sulphatase inhibitors, sulphamatase inhibitors and mixtures thereof.

Examples of these enzyme inhibitors, together with the relevant enzymes whose activity they inhibit, can be classified as follows:

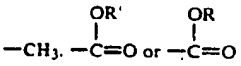
Chemical Class	Enzyme(s) Inhibited
(a) Anions (as soluble metal or ammonium salts)	
sulphate	idurono-sulphate sulphatase; sulphatases A and B; heparin sulphamatase; N-acetylglucosamine-6-sulphate sulphatase
sulphite	sulphatase A; heparin sulphamatase
pyrophosphate	sulphatase A; chondroitin-6-sulphatase; heparin sulphamatase
fluoride	sulphatase A; heparin sulphamatase
borate	- heparin sulphamatase
chloride	sulphatase B; chondroitin-6-sulphatase
gluconate	- sulphatase B

Of the above anion inhibitors of sulphatase A or B, particularly preferred examples are sulphate and gluconate, especially in the form of magnesium sulphate and zinc gluconate respectively.

(b) Aldonolactones and esterified aldonolactones having the structure:



where
A^1 and A^6 are —H,



B is OR" or a lactone linkage to position 1 or 6, or —$NHCOCH_3$
and where R is -H or C_2 to C_8 alkyl,
R' is the remainder of the molecule joined through another C atom at positions 2 to 5 to form a lactone,
R" is —H or C_2 (ie acetyl) to C_4 acyl of either configuration with respect to the backbone of this molecule.

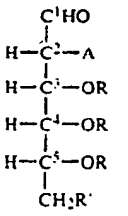
Preferred examples of aldonolactones which inhibit the exoglycosidases, as specified, are as follows:

	Enzyme(s) inhibited
L-Galactono-1,4-lactone	β-galactosidase β-N-acetylhexosaminidase
L-Arabino-1,5-lactone	β-galactosidase
D-Fucono-1,5-lactone	β-galactosidase
D-Glucaro-1,4-lactone	β-glucuronidase α-L-iduronidase
D-Glucurono-6,3-lactone	β-glucuronidase
Galactaric acid lactone	β-glucuronidase α-L-iduronidase
2-Acetamido-2-deoxygluconolactone	β-N-acetylhexosaminidase
2-Acetamido-2-deoxygalactonolactone	β-N-acetylhexosaminidase
D-Glucaro-1,4:6,3-dilactone	β-glucuronidase α-L-iduronidase
L-Idaro-1,4-lactone	α-L-iduronidase

Preferred examples of esterified forms of aldonolactones which give a more sustained inhibitory effect are:

2,3,5-Tri-O-acetyl-D-glucaro-1,4-lactone	β-glucuronidase α-L-iduronidase
2,5-Di-O-acetyl-D-glucaro-1,4:6,3-dilactone	β-glucuronidase α-L-iduronidase

(c) Monosaccharides and esterified monosaccharides having the structure:



where

A is —OR or —NHCOCH$_3$
R is —H, —SO$_3$M, C$_2$ (ie acetyl) to C$_4$ *acyl*
R' is —H or —OR
M is —H or a metal cation.

Functional groups can be in either configuration with respect to the backbone of the above molecule.

Preferred examples of monosaccharides and esters thereof which inhibit exoglycosidases or a sulphatase, as specified, are as follows:

Monosaccharide/esters	Enzymes(s) inhibited
N-Acetylglucosamine	α-N-acetylglucosaminidase β-galactosidase β-N-acetylhexosaminidase
N-Acetylgalactosamine	β-galactosidase β-N-acetylhexosaminidase
D-Galactosamine	β-N-acetylhexosaminidase
D-Glucosamine-3-sulphate	Sulphatase 'B'
N-Acetylmannosamine	α-N-acetylglucosaminidase

(d) Piperidines having the structure:

where
LA is —H, —OR' or

R is —H, C$_2$ to C$_8$ alkyl or diamino-pyrimidine N-oxide
R' is —H or C$_2$ (ie acetyl) to C$_4$ acyl;
substituent groups A can be identical or can be represented by 2 or 3 of the groups defined above on the same ring structures. They can also be in either configuration with respect to the plane of the ring.

Preferred examples of piperidines which inhibit exoglycosidases, as specified, are as follows:

Minoxidil which inhibits the enzyme β-glucuronidase and

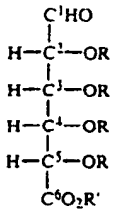
2(S)-Carboxy-3(R),4(R),5(S)-trihydroxypiperidine which inhibit the enzymes β-glucuronidase and α-L-iduronidase.

(e) examples of substances which inhibit the activity of the endoglycosidase hyaluronate endoglycosidaminidase are:
Phosphorylated hesperidin
sodium aurothiomalate
substituted thiosemicarbazone indoles, and
mixtures thereof.

The glycosaminoglycan chain cellular uptake inhibitors

According to a further embodiment of the invention, the composition comprises an inhibitor of cellular uptake of glycosaminoglycan chains which prevents recognition and binding events at the cell surface by competing with glycosaminoglycan chains, or by modification of the chains so that they are no longer recognised by the cell.

An example of this class of inhibitors is given by hexuronic acid and esters thereof which may be represented by the generic structure:



where R is —H, —SO$_3$M, C$_2$ (ie acetyl) to C$_4$ acyl; R' is —H or C$_2$ to C$_8$ alkyl.

Functional groups can be in either configuration with respect to the backbone of the above molecule.

Preferred inhibitors belonging to this class are glucuronic acid, iduronic acid and esters thereof.

The total amount of chemical inhibitor present in the composition according to the invention is sufficient to increase hair growth in the rat, the model selected for this test, when said composition is applied topically thereto, by at least 10% more than that obtainable using a control composition from which the said inhibitors have been omitted.

Preferably, the amount of chemical inhibitor should be sufficient to increase hair growth in the rat by at least 20%, more preferably by at least 30%, most preferably by at least 40% and ideally by at least 50%.

The sufficient amount will depend on the effectiveness of a chemical inhibitor, some being more effective than others, but in general, an amount of from 0.0001 to 99%, preferably from 0.1 to 20% by weight of the composition will provide an adequate dose to the skin after topical application.

Compositions containing minoxidil

Minoxidil is a weak inhibitor of β-glucuronidase activity and accordingly, when minoxidil is present in the composition, then there is also present a second chemical inhibitor and/or an activity enhancer.

Particularly preferred mixtures of minoxidil and a second chemical inhibitor include the following:
Minoxidil and Zinc gluconate
Minoxidil and Magnesium sulphate
Minoxidil and D-glucaro-1,4-lactone
Minoxidil and 1,10-phenanthroline
Minoxidil and D-glucosamine-3-sulphate
Minoxidil and L-idaro-1,4-lactone
Minoxidil and L-galactono-1,4-lactone
Minoxidil and 2-acetamido-2-deoxygluconolactone
Minoxidil and D-glucaro-1,4:6,3-dilactone
Minoxidil and 2,3,5-tri-O-acetyl-D-glucaro-1,4-lactone
Minoxidil and N-acetylglucosamine
Minoxidil and N-acetylmannosamine
Minoxidil and phosphorylated hesperidin
Minoxidil and glucuronic acid

When minoxidil is the sole chemical inhibitor present in the composition according to the invention, then a special condition on its use in accordance with the invention prevails in that the activity enhancer which must accompany minoxidil, preferably in an amount sufficient to enhance significantly the hair growth-activity of minoxidil, in the composition, is chosen from a limited selection of materials, referred to in detail later

in this specification, namely certain penetration enhancers and certain cationic polymers.

The Vehicle

The composition according to the invention also comprises a solid, semi-solid or liquid cosmetically and/or physiologically acceptable vehicle, to enable the inhibitor to be conveyed to the skin at an appropriate dilution. The nature of the vehicle will depend upon the method chosen for topical administration of the composition. The vehicle can itself be inert or it can possess physiological or pharmaceutical benefits of its own.

The selection of a vehicle for this purpose presents a wide range of possibilities depending on the required product form of the composition. Suitable vehicles can be classified as described hereinafter.

It should be explained that vehicles are substances which can act as diluents, dispersants, or solvents for the chemical inhibitors which therefore ensure that they can be applied to and distributed evenly over the hair and/or scalp at an appropriate concentration. The vehicle is preferably one which can aid penetration of the inhibitors into the skin to reach the immediate environment of the hair follicle. Compositions according to this invention can include water as a vehicle, and/or at least one cosmetically acceptable vehicle other than water.

Vehicles other than water that can be used in compositions according to the invention can include solids or liquids such as emollients, solvents, humectants, thickeners and powders. Examples of each of these types of vehicles, which can be used singly or as mixtures of one or more vehicles, are as follows:

Emollients, such as stearyl alcohol, glyceryl monoricinoleate, glyceryl monostearate, propane-1,2-diol, butane-1,3-diol, mink oil, cetyl alcohol, ispropyl isostearate, stearic acid, isobutyl palmitate, isocetyl stearate, oleyl alcohol, isopropyl laurate, hexyl laurate, decyl oleate, octadecan-2-ol, isocetyl alcohol, cetyl palmitate, dimethylpolysiloxane, di-n-butyl sebacate, isopropyl myristate, isopropyl palmitate, isopropyl stearate, butyl stearate, polythylene glycol, triethylene glycol, lanolin, sesame oil, coconut oil, arachis oil, castor oil, acetylated lanolin alcohols, petroleum, mineral oil, butyl myristate, isostearic acid, palmitic acid, isopropyl linoleate, lauryl lactate, myristyl lactate, decyl oleate, myristyl myristate;

Propellants, such as trichloroflucromethane, dichlorodifluoromethane, dichlorotetrafluoroethane, monochlorodifluoromethane, trichlorotrifluoroethane, propane, butane, isobutane, dimethyl ether, carbon dioxide, nitrous oxide;

Solvents, such as ethyl alcohol, methylene chloride, isopropanol, castor oil, ethylene glycol monoethyl ether, diethylene glycol monobutyl ether, diethylene glycol monoethyl ether, dimethyl sulphoxide, dimethyl formamide, tetrahydrofuran;

Humectants, such as glycerin, sorbitol, sodium 2-pyrrolidone-5-carboxylate, soluble collagen, dibutyl phthalate, gelatin;

Powders, such as chalk, talc, fullers earth, kaolin, starch, gums, colloidal silicon dioxide, sodium polyacrylate, tetra alkyl and/or trialkyl aryl ammonium smectites, chemically modified magnesium aluminium silicate, organically modified montmorillonite clay, hydrated aluminium silicate, fumed silica, carboxyvinyl polymer, sodium carboxymethyl cellulose, ethylene glycol monostearate.

The amount of vehicle in the composition, including water if present, should preferably be sufficient to carry at least a portion of a selected chemical inhibitor to the skin in an amount which is sufficient effectively to enhance hair growth. The amount of the vehicle can comprise the balance of the composition, particularly where little or no other ingredients are present in the composition. Accordingly, the vehicle or vehicles can comprise from 1 to 99.99%, preferably from 50 to 99.5% and ideally from 90 to 99% by weight of the composition.

Perfume

The composition according to the invention can also optionally comprise a perfume in an amount sufficient to make the composition acceptable to the consumer and pleasant to use. Usually, the perfume will form from 0.01 to 10% by weight of the composition.

Activity Enhancer

The composition according to the invention can also optionally comprise an activity enhancer, especially when the chemical inhibitor is a weak inhibitor.

The activity enhancer can be chosen from a wide variety of molecules which can function in different ways to enhance the hair growth effects of the chemical inhibitor. Particular classes of activity enhancers include other hair growth stimulants, penetration enhancers and cationic polymers, whose presence can further improve the delivery of the chemical inhibitor through the stratum corneum to its site of action in the immediate environment of the hair follicle.

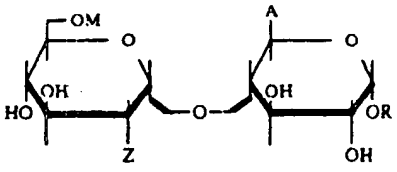
Some activity enhancers can also function as vehicles for the chemical inhibitor.

(a) Other Hair Growth Stimulants

Examples of other substances which themselves possess the ability to stimulate or increase hair growth include, for example;

Benzalkonium chloride
Benzethonium chloride
Phenol
Estradiol
Diphenhydramine hydrochloride
Chlorpheniramine maleate
Chlorophyllin derivatives
Cholesterol
Salicylic acid
Cystine
Red pepper tincture
Benzyl nicotinate
dl-Menthol
Peppermint oil
Calcium pantothenate
Panthenol
Castor oil
Hinokitiol
Prednisolone
Resorcinol

Further substances which themselves possess the ability to increase the rate of terminal hair growth include: α-1,4esterified disaccharides described by Choay S.A. in EP-A-O 064 012, having the structure:



where

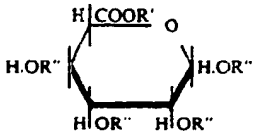
Z represents a functional nitrogen group, such as an azide or a group having the structure —NHB, in which B represents —H or a functional group such as acetyl or sulphate as a salt with an organic or mineral cation;

M represents —H or SO_3M_1, where M_1 is an organic or metallic cation, particularly an alkali metal; or an acetyl group;

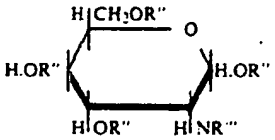
R represents a C_1 to C_4 alkyl radical, especially methyl; or an aryl radical;

A represents a functional group such as an acid or —$COOR_1$, where R_1 represents —H or a C_1 to C_4 alkyl radical, especially methyl; or a metal, especially an alkali metal;

esterified oligosaccharides as described by Unilever in EP-A-0 211 610, including at least one esterified disaccharide unit consisting of a uronic acid residue having the structure:

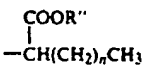


and a hexosamine residue having the structure:



where

R'is —H, C_3 to C_{10} alkyl or



R" is —H, C_1 to C_4 alkyl, —$CO(CH_2)_mCH_3$, —SO_3M,

R'" is —H, —$CO(CH_2)_mCH_3$, or —SO_3M,

M is —H, or a metallic or organic cation

n is 0 or an integer of from 1 to 7, and

m is 0 or the integer 1 or 2;

the groups designated R" being the same or different, one R" group from each pyranose ring structure being linked by a glycosidic linkage having the configuration α-1,3, α1,4, β-1,3 or β-1,4; and the —COOR', —CH_2OR" and —OR" groups being of either configuration with respect to the pyranose rings;

Minoxidil glucuronides, as described by Unilever in EP-O 242 967,

Minoxidil sulphates, as described by The Upjohn Co. in WO 86/04231.

(b) Penetration Enhancers

As has been stated earlier, the presence of a penetration enhancer can potentiate the benefit of the chemical inhibitor, by improving its delivery through the stratum corneum to its site of action in the immediate environment of the hair follicle close to the dermal papilla.

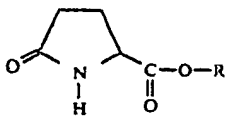
The penetration enhancer can accordingly function in a variety of ways. It can for example, improve the distribution of the hair growth promoter on the skin surface or, it can increase its partition into the skin from the composition when applied topically, so aiding its passage to its site of action. Other mechanisms enhancing the benefit of the chemical inhibitor may also be involved.

Examples of penetration enhancers include:

2-methyl propan-2-ol
Propan-2-ol
Ethyl-2-hydroxypropanoate
Hexan-2,5-diol
POE(2) ethyl ether
Di(2-hydroxypropyl) ether
Pentan-2,4-diol
Acetone
POE(2) methyl ether
2-hydroxypropionic acid
2-hydroxyoctanoic acid
Propan-1-ol
1,4 Dioxane
Tetrahydrofuran
Butan-1,4-diol
Propylene glycol dipelargonate
Polyoxypropylene 15 stearyl ether
Octyl alcohol
POE ester of oleyl alcohol
Oleyl alcohol
Lauryl alcohol
Dioctyl adipate
Dicapryl adipate
Diisopropyl adipate
Diisopropyl sebacate
Dibutyl sebacate
Diethyl sebacate
Dimethyl sebacate
Dioctyl sebacate
Dibutyl suberate
Dioctyl azelate
Debenzyl sebacate
Dibutyl phthalate
Dibutyl azelate
Ethyl myristate
Dimethyl azelate
Butyl myristate
Dibutyl succinate
Didecyl phthalate
Decyl oleate
Ethyl caproate
Ethyl salicylate
Isopropyl palmitate
Ethyl laurate
2-ethyl-hexyl pelargonate
Isopropyl isostearate
Butyl laurate
Benzyl benzoate
Butyl benzoate
Hexyl laurate
Ethyl caprate
Ethyl caprylate

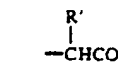
Butyl stearate
Benzyl salicylate
2-hydroxypropanoic acid
2-hyroxyoctanoic acid,

Yet further penetration enhancers include esters of pyroglutamic acid having the structure:

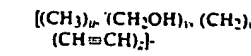


(1)

where R is C_1 to C_{30} alkyl, or



and where R' and R" are the same or different and are each represented by H or the grouping.



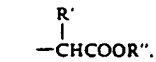
(2)

where
u is zero or 1
v is zero, or the integer 1 or 2,
w is zero, or an integer of from 1 to 21
x is zero, or an integer of from 1 to 4,
y is zero, or the integer 1 or 2,
z is zero, or an integer of from 1 to 22, and
u+v+w+x+y+z is an integer of from 1 to 22;
provided that when the subgrouping (CH=CH) is present, then the total number of carbon atoms in said grouping is from 10 to 22.

Examples of suitable esters of pyroglutamic acid where R in structure (1) is C_1 to C_{30} alkyl are:
pyroglutamic acid methyl ester
pyroglutamic acid ethyl ester
pyroglutamic acid n-propyl ester
pyroglutamic acid n-butyl ester
pyroglutamic acid n-heptyl ester
pyroglutamic acid n-octyl ester
pyroglutamic acid n-nonyl ester
pyroglutamic acid n-decyl ester
pyroglutamic acid n-undecyl ester
pyroglutamic acid n-dodecyl ester
pyroglutamic acid n-tridecyl ester
pyroglutamic acid n-tetradcyl ester
pyroglutamic acid n-hexadecyl ester
pyroglutamic acid n-octadecyl ester
pyroglutamic acid n-eicosyl ester
pyroglutamic acid iso-propyl ester
pyroglutamic acid 2-methylhexyl ester
pyroglutamic acid 2-ethylhexyl ester
pyroglutamic acid 3,7-dimethyloctyl ester
pyroglutamic acid 2-hexyldecyl ester
pyroglutamic acid 2-octyldodecyl ester
pyroglutamic acid 2,4,4-trimetyl-1-pentane ester
pyroglutamic acid methyloctyl ester

Particularly preferred esters of this group are those where R in structure (1) is C_1 to C_{14} alkyl, (linear or branched), especially C_1 to C_6 (linear or branched).

Further examples of preferred esters of pyroglutamic acid, where R in structure (1) is



are those where R' and/or R" having the structure shown for grouping (2), include straight and branched chain, saturated or unsaturated aliphatic groups having from 1 to 22 carbon atoms, such as the alkyl groups:
methyl
ethyl
propyl
iso-propyl
butyl
iso-butyl
n-valeryl
iso-valeryl
n-caproyl
n-heptyl
n-caprylyl
n-capryl
lauryl
myristyl
palmityl
stearyl, and
arachidyl.
and the C_{10-22} alkenyl groups:
linoleyl
linolenyl
γ-linolenyl
arachidonyl, and
Columvinyl.

Further examples of the grouping (2) also include hydroxyalkyl groups having from 1 to 22 carbon atoms, such as:
hydroxymethyl
2-hydroxyethyl
2-hydroxy-n-propyl
3-hydroxy-n-propyl
2-hydroxy-n-butyl
3-hydroxy-n-butyl
4-hydroxy-n-butyl
5-hydroxy-n-valeryl
6-hydroxy-n-caproyl
2,3-dihydroxy-n-propyl
2,3-dihydroxy-n-butyl
12-hydroxystearyl.

It is to be understood that the above list is not exhaustive, there being many other examples of alkyl or substituted alkyl groups expressed by the above generic grouping (2).

Further specific examples of esters of pyroglutamic acid which are particularly suited to use as penetration enhancers are:
2-[pyroglutamoyloxy]-propionic acid
methyl-2-[pyroglutamoyloxy]-acetate
ethyl-2-[pyroglutamoyloxy]-n-propionate
ethyl-2-[pyroglutamoyloxy]-n-butyrate
ethyl-2-[pyroglutamoyloxy]-iso-butyrate
ethyl-2-[pyroglutamoyloxy]-n-valerate
ethyl-2-[pyroglutamoyloxy]-n-caproate
ethyl-2-[pyroglutamoyloxy]-n-heptylate
ethyl-2-[pyroglutamoyloxy]-n-caprylate
ethyl-2-[pyroglutamoyloxy]-n-pelargonate
ethyl-2-[pyroglutamoyloxy]-3-hydroxybutyrate
iso-propyl-2-[pyroglutamoyloxy]-n-propionate
iso-propyl-2-[pyroglutamoyloxy]-n-caprylate
n-propyl-2-[pyroglutamoyloxy]-n-propionate

n-propyl-2-[pyroglutamoyloxy]-n-caprylate
stearyl-2-[pyroglutamoyloxy]-n-propionate
12-hydroxystearyl-2-[pyroglutamoyloxy]-n-propionate
stearyl-2-[pyroglutamoyloxy]-n-stearate
palmityl-2-[pyroglutamoyloxy]-n-propionate
linoleyl-2-[pyroglutamoyloxy]-n-propionate
linoleyl-2-[pyroglutamoyloxy]-n-caprylate
lauryl-2-[pyroglutamoyloxy]-n-caprylate
stearyl-2-[pyroglutamoyloxy]-n-caprylate
glyceryl mono(2-[pyroglutamoyloxy]-n-propionate)
glyceryl mono(2-[pyroglutamoyloxy]-n-caprylate), and
glyceryl di(2-[pyroglutamoyloxy]-n-propionate).

It is to be understood that the above lists of specific examples of esters of pyroglutamic acid are not exhaustive, there being many other examples expressed by the generic structure of these esters.

Further examples of penetration enhancers include:
Dimethyl sulphoxide
N,N-Dimethyl acetamide
N,N-Dimethyl formamide
2-Pyrrolidone
1-Methyl-2-pyrrolidone
5-Methyl-2-pyrrolidone
1,5-Dimethyl-2-pyrrolidone
1-Ethyl-2-pyrrolidone
Phosphine oxides
Sugar esters
Tetrahydrofurfural alcohol
Urea
Diethyl-m-toluamide, and
1-Dodecylazacycloheptan-2-one

Further examples of penetration enhancers include surface active agents, preferred examples of which include:

(i)

Anionic surface active agents, such as metallic or alkanolamine salts of fatty acids for example sodium laurate and triethanolamine oleate;

alkyl benzene sulphonates, for example triethanolamine dodecyl benzene sulphonate;
alkyl sulphates, for example sodium lauryl sulphate;
alkyl ether sulphates, for example sodium lauryl ether sulphate [2 to 8 EO];
sulphosuccinates, for example sodium dioctyl sulphonsuccinate;
monoglyceride sulphates, for example sodium glyceryl monostearate monosulphate;
isethionates, for example sodium isethionate;
methyl taurides, for example Igepon T;
acylsarcosinates, for example sodium myristyl sarcosinate;
acyl peptides, for example Maypons and Lamepons;
acyl lactylates,
polyalkoxylated ether glycollates, for example trideceth-7 carboxylic acid;
phosphates, for example sodium dilauryl phosphate.

(ii)

Cationic surface active agents, such as amine salts, for example sapamin hydrochloride;
quartenary ammonium salts, for example Quaternium 5, Quaternium 31 and Quaternium 18;

(iii)

Amphoteric surface active agents, such as imidazol compounds, for example Miranol;
N-alkyl amino acids, such as sodium cocaminopropionate and asparagine derivatives;
betaines, for example cocoamidopropylbetaine

(iv)

Nonionic surface active agents, such as fatty acid alkanolamides, for example oleic ethanolamide;
esters of polyalcohols, for example Span;
polyglycerol esters, for example that esterified with C_{12-18} fatty acids and one or several OH groups;
polyalkoxylated derivatives, for example polyoxypolyoxyethylene stearate, and octylphenoxy polyethoxyethanol (TRITON X-100);
ethers, for example polyoxyethylene lauryl ether;
ester ethers, for example Tween;
amine oxides, for example coconut and dodecyl dimethyl amine oxides.

Mixtures of two or more of the above surface active agents can be employed in the composition according to the invention.

(c) cationic polymers chosen from:
Guar Hydroxypropyltrimonium chloride
Quaternium-19
Quaternium-23
Quaternium-40
Quaternium-57
Poly(dipropyldiallylammonium chloride)
Poly(methyl-β-propaniodiallylammonium chloride)
Poly(diallylpiperidinium chloride)
Poly(vinyl pyridinium chloride)
Quaternised poly (vinyl alcohol)
Quaternised poly (dimethylaminoethylmethacrylate); and
mixtures thereof

It is to be understood that even when a strong chemical inhibitor is employed, then it is also desirable, though not essential, to incorporate an activity enhancer in the composition according to the invention, in order further to enhance its benefit in increasing the hair growth.

The amount of activity enhancer, when employed in accordance with the invention, will normally be from 0.1 to 50%, preferably from 0.5 to 25% and most preferably from 0.5 to 10% by weight of the composition.

Further preferred embodiments of the invention

Further preferred embodiments of the invention are those where the composition according to the invention comprises an activity enhancer in addition to at least one chemical inhibitor.

Particularly preferred mixtures of chemical inhibitors and activity enhancers include the following, where minoxidil as a less effective chemical inhibitor, as herein defined, should be employed in compositions according to the invention with an activity enhancer.

Accordingly, preferred mixtures are:
Minoxidil and diisopropyl sebacate
Minoxidil and pyroglutamic acid methyl ester
Minoxidil and pyroglutamic acid n-propyl ether
Minoxidil and 2[pyroglutamoyloxy]-propionic acid
Minoxidil and ethyl-2-[pyroglutamoyloxy]-n-propionate
Minoxidil and 2-hydroxy octanoic acid

Other hair growth promoter adjuncts

The composition according to the invention can also contain adjuncts other than those already mentioned, depending on the form of the intended product. It is, for example, possible to include antiseptics, preservatives,

antioxidants, emulsifiers and colouring agents, which can improve the stability and consumer appeal of the composition.

The composition according to the invention can also be employed as a vehicle for a wide variety of cosmetically or pharmaceutically active ingredients, particularly ingredients which have some beneficial effect other than the promotion of hair growth when applied to the skin.

Process

The invention also provides a process for the preparation of a composition suitable for topical application to mammalian skin or hair which comprises mixing a chemical inhibitor as herein defined, with a suitable vehicle to provide a composition according to the invention, in which the inhibitor forms from 0.0001 to 99% by weight of the composition.

Product Form and Container

The compositions of the invention can be formulated as liquids, for example as a lotion, shampoo, milk or cream for use in conjunction with an applicator such as a roll-ball applicator, or a spray device such as an aerosol can containing propellant, or a container fitted with a pump to dispense the liquid product. Alternatively, the compositions of the invention can be solid or semi-solid, for example sticks, creams or gels, for use in conjunction with a suitable applicator or simply a tube, bottle or lidded jar, or as a liquid-impregnated fabric, such as a tissue wipe.

The invention accordingly also provides a closed container containing a composition as herein defined.

Use of the Chemical Inhibitor for Inducing, Maintaining or Increasing Hair Growth

The invention also provides for the use of a chemical inhibitor, as herein defined, for topical application to mammalian skin or hair for inducing, maintaining or increasing hair growth.

The compositions according to the invention are primarily intended for topical application to the scalp of the human subject, particularly where the head is already bald or balding, in order to promote the regrowth of terminal hair. The compositions can also be applied profilactically to the hair and hence the scalp to reduce or prevent the onset of baldness.

The amount of the composition and the frequency of application to the hair and/or scalp can vary widely, depending on personal needs, but it is suggested as an example that topical application of from 0.1 to 5g daily containing from 0.00001 to 1 g of a selected chemical inhibitor over the period of at least six months will in most cases result in an improvement in hair growth.

EVALUATION OF EFFICACY OF CHEMICAL INHIBITORS USING THE RAT MODEL

(i) Measurement of hair growth using the rat model

The effect of compounds on hair growth was assessed using male rats as an animal model as follows. In each of the comparisons reported below, 10 rats were used.

A small patch of normal skin (4cm ×4cm) on the upper back of each rat was clipped at the start of the experiment and a hair growth stimulant composition (or a control) applied twice daily topically to the clipped area. Hair was clipped from the area of the patch twice weekly, collected and weighed at each time point, and cumulative hair weight calculated. From these data, it was possible to estimate the effect of a chemical inhibitor as a test compound on the amount and duration of hair growth during the experiment. A positive response, ie. an increase of at least 10% by weight of hair, compared with a control, indicates the potential of the test substance to prevent hair loss and/or reverse baldness in human subjects.

(ii) Validation of rat model for hair growth using Minoxidil

The rat model was validated by showing that topical application of a known promoter of human hair regrowth, namely 2% (w/v) minoxidil in a vehicle of 70% ethanol, 20% water and 10% propylene glycol, caused a significant increase of 55% in hair growth as shown below:

TABLE 1

Treatment	Mean Cumulative Hair weight (mg) ± sd. after 45 days	Significance Level (vs vehicle)
2% minoxidil	599.2 ± 85.1	p = 0.001*
Vehicle (control)	387.3 ± 75.9	

*statistically significant

(iii) Measurement of hair growth following topical application of D-glucaro-1,4-lactone as enzyme inhibitor

Topical treatment with a composition according to the invention was found to stimulate hair growth. In this example, the effect of topical application of D-glucaro-1,4-lactone, an inhibitor of β-glucuronidase is shown. The test solution in this experiment contained approximately 7% (w/v) of the glucarolactone in the form of an equilibrium mixture prepared from boiled calcium glucarate. The vehicle was 33% (v/v) ethanol containing 50mM Na citrate at pH 4.2. Test or control solutions (0.3ml) were applied twice-daily to the clipped site; the hair growth results are shown below in Table 2.

TABLE 2

Treatment	Mean Cumulative Hair weight (mg) ± sd. after 45 days	Significance Level (vs vehicle)
7% Glucarolactone	482.7 ± 58.4	p < 0.05*
Vehicle (control)	427.2 ± 58.7	

*statistically significant

In addition to demonstrating a statistically significant stimulation of hair growth (a 13% increase) as shown in Table 2, glucarolactone has been consistently found to advance the onset of anagen, thus reducing the amount of time spent in the resting stage of hair cycle.

(iv) Synergistic interaction of D-glucaro-1,4-lactone and minoxidil in hair growth

In other experiments, glucarolactone has been found to display a synergistic effect on hair growth in combination with a low concentration of minoxidil. Both glucarolactone and minoxidil are β-glucuronidase inhibitors. This effect is illustrated in Table 3 below, in which the vehicle was 33% v/v ethanol in 50mM sodium citrate, pH4.2:

TABLE 3

Treatment	Mean Cumulative hair weight (mg) ± sd. after 45 days	Signif-icance level (vs vehicle)	Increase in hair growth (%) (Test vs control)
7% glucarolactone (GL)	482.7 ± 58.4	$p < 0.05$*	13
0.2% minoxidil (M)	465.8 ± 48.8	$p > 0.1$	9
7% GL + 0.2% M	561.1 ± 57.7	$p = 0.001$*	31
Vehicle (control)	427.2 ± 58.7		

*statistically significant

From these results, it can be seen that the hair growth properties of minoxidil alone (9% increase in hair growth), can be greatly enhanced when the glucarolactone is present (31% increase in hair growth), thus making possible the use of a lower than usual concentration of minoxidil (for example, 0.2% by weight which is water soluble, instead of 2% by weight which is not) without diminishing its ability to stimulate hair growth. The statistical significance of this synergistic effect can be deduced from the results shown in Table 3 above, when it is realised that the mean of GL+M was compared with either GL ($p < 0.01$) or M ($p=0.001$) alone.

A further advantage of using a composition containing a lower than usual concentration of minoxidil is the enhanced in-use safety margin, bearing in mind possible contra-indications which alledgedly follow topical application of higher concentrations of minoxidil.

(v) Influence of 1-methylpyrrolidone as activity enhancer in the stimulation of hair growth with glucarolactone

In a further experiment, glucarolactone was tested in the presence of an activity enhancer, 1-methylpyrrolidone. Again, a significant increase in hair weight was obtained, as shown below in Table 4, in which the vehicle was 33% v/v aqueous ethanol containing 50mM Na citrate buffer pH4.2 and 10% w/v 1-methylpyrrolidone.

TABLE 4

Treatment	Mean Cumulative Hair Weight (mg) ± sd. after 46 days	Significance Level (vs vehicle)
7% glucarolactone	706.2 ± 86.6	$p < 0.01$*
vehicle (control)	611.1 ± 48.1	

*statistically significant

This represents a 15% increase in hair growth.

(vi) Influence of the wetting agent Triton X-100 as an activity enhancer in the stimulation of hair growth with glucarolactone

In a further experiment, the inclusion of a surface active agent, Triton X-100 was found to provide a particularly advantageous activity enhancer for glucarolactone, as shown below in Table 5, in which the vehicle was 20% v/v ethanol containing 50mM sodium citrate, pH4.2 and 0.1% w/v Trion X-100.

Treatment	Mean Cumulative Hair Weight (mg) ± sd. after 43 days	Significance Level (vs vehicle)
7% glucarolactone	573.3 ± 82.5	$p = 0.001$*
vehicle (control)	412.3 ± 57.5	

*statistically significant

This represents a 39% increase in hair growth.

(vii) Influence of Zinc gluconate as an inhibitor of Sulphatase B in the stimulation of hair growth

In another experiment, the effect of sulphatase B inhibitor, zinc gluconate was examined and found to produce a significant increase in hair weight as shown below in Table 6, in which the vehicle was 20% aqueous ethanol.

TABLE 6

Treatment	Mean Cumulative Hair Weight (mg) ± sd. after 45 days	Significance Level (vs vehicle)
2% (w/v) zinc gluconate	460.9 ± 45.7	$p < 0.05$*
vehicle (control)	397.8 ± 56.3	

*statistically significant

This represents a 16% increase in hair growth.

Assay of enzyme activity and cellular uptake, and inhibition thereof with the chemical inhibitor

It is a feature of the invention that the chemical inhibitor is one whose inhibition of proteoglycanase activity, glycosaminoglycanase activity or cellular uptake of glycosaminoglycans chains is such that a 1 mM aqueous solution of the inhibitor reduces said activity or said cellular uptake by more that 50% as measured by an appropriate assay.

For chemical inhibitors which are less effective in that at the same concentration, they reduce said activity or said cellular uptake by from 5 to 50%, it is then necessary to include also a second chemical inhibitor and/or an activity enhancer as herein defined, which will not necessarily increase said activity or said cellular uptake, as measured in vitro, but which will nevertheless further enhance hair growth, often synergistically.

In each of the assays referred to herein, the chemical inhibitor was tested at a pH close to the optimum pH value of the relevant enzyme, and under conditions of saturating substrate concentration, to ensure that V_{max} was obtained in the controls.

The relevant assays employed to assess the ability of chemical inhibitors to inhibit enzyme activity or cellular uptake are as follows:

1. Proteoglycanase assay

The degradation of proteoglycan by proteoglycanase and its inhibition was determined using the method described by Nagase & Woessner in Analyt. Biochem., 107, 385 (1980).

2. Glycosaminoglycanase assay

In view of the complexity of the glycosaminoglycan chain, several different enzymes are known to cleave this chain at different points. Glycosaminoglycanases, can accordingly be classified into exoglycosidases, endoglycosidases, sulphatases and sulphamatases. Different assay methods were used for each of these classes. These methods are outlined below.

2.1 Exoglycosidases

2.1.1 β, N-acetylhexosaminidase

2.1.2 β-glucuronidase

2.1.3 β-galactosidase.

2.1.4 α-N-acetylglucosaminidase

The activity of each of these four exoglycosidases was measured using a method described in "Lysosomes, A Laboratory Handbook", edited by Dingle J.T., Second Edition, (1977) at page 118.

2.1.5 α-L-iduronidase

The activity of α-L-iduronidase was measured using Method II described by Dingle J.T. [Ibid., at page 119].

2.2 Endoglycosidase

2.2.1 Hyaluronate endoglycosidaminidase

The activity of hyaluronate endoglycosaminidase, also known as hyaluronidase was assayed by the method described by Dingle J.T [Ibid., at page 116].

2.2.2 Heparan sulphate endoglycosidase

The activity of heparan sulphate endoglycosidase was assayed by the method described by Hook et al., (1975) in Biochem. Biophys. Res. Commun. 67, 1422–1428.

3. Sulphatases and Sulphamatases

3.1 Sulphatase A and Sulphatase B

The activity of sulphatase A and B was measured using the method described by Dingle J.T. [Ibid., at page 115].

3.2 Chondroitin-6-Sulphatase

The activity of chondroitin-6-sulphatase was measured using the method reported by Singh et al (1976) in J. Clin. Invest. 57, 1036–1040.

3.3 Idurono-sulphate sulphatase

The activity of idurono-sulphate sulphatase was measured using the method reported by Lim et al (1974) in Carbohyd. Res. 37, 103–109.

3.4 Heparin Sulphamatase

The activity of heparin sulphamatase was measured using the method reported by Friedman and Arsenis (1972) in Biochem. Biophys. Res. Commun. 48, 1133–1139.

3.5 N-Acetylglucosamine-sulphate sulphatase

The activity of N-acetylglucosamine sulphate sulphatase was measured using the method reported by Habuchi et al (1979) in J.Biol. Chem., 254 7570–7578.

4. Inhibition of cellular uptake of glycosaminoglycan chains

The inhibition of cellular uptake of glycosaminoglycan chains was measured using the method reported by Eskild et al., (1986) in Int. J. Biochem. 18, 647–651.

The inhibitory effect of minoxidil on β-glucuronidase activity

The ability of minoxidil to inhibit the activity of β-glucuronidase was evaluated by the method reported by Dingle J.T. [Ibid., page 118] as described herein.

The results using different concentrations of minoxidil when incubated with a mixture of this enzyme and the nitrophenyl glucuronide substrate were as follows:

Minoxidil concentration		% inhibition of
mg/ml	mM	β-glucuronidase
0.05	0.24	2
0.4	1.9	12
0.8	3.8	23

The percent inhibition of a 1mM concentration of minoxidil is accordingly 6%. This confirms that minoxidil is a weak enzyme inhibitor and, in accordance with the composition of the invention, when the inhibitory effect of an inhibitor is between 5 and 50%, as herein defined, then it is necessary to include in a composition containing minoxidil, a second chemical inhibitor and/or an activity enhancer.

The inhibitory effect of glucuronic acid and glucurono-6,3-lactone on β-glucuronidase activity

The ability of glucuronic acid and glucurono-6,3-lactone to inhibit the activity of β-glucuronidase was also evaluated by the method reported by Dingle J.T. [Ibid., page 118].

The results when the acid or the lactone were incubated with a mixture of this enzyme and the nitrophenyl glucuronide substrate were as follow:

Inhibitor	Inhibitor concentration mg/ml	mM	% inhibition of β-glucuronidase
Glucuronic acid	0.2	1.03	20
Glucurono-6,3-lactone	0.2	1.14	51

The percentage inhibition of a 1mM concentration of glucuronic acid is accordingly 19.4 and that of glucurono-6,3-lactone is 44.7. This confirms that both glucuronic acid and glucurono-6,3-lactone are weak enzyme inhibitors and, in accordance with the composition of the invention, when the inhibitory effect of an inhibitor is between 5 and 50%, as herein defined, then it is necessary to include in such a composition a second chemical inhibitor and/or an activity enhancer.

EXAMPLES

The invention is illustrated by the following examples:

EXAMPLE 1

This Example illustrates a lotion according to the invention which is suitable for topical application to the scalp in order to promote hair growth.

The lotion has the following formulation:

	% w/w
L-Galactono-1,4-lactone	0.1
ethanol	99.995
perfume	q.s.

EXAMPLE 2

This Example illustrates a hair tonic which is suitable for application to hair or scalp.

The hair tonic has the following formulation:

	% w/w
L-Arabino-1,5-lactone	0.8

-continued

	% w/w
ethanol	50
water	49
perfume	q.s.

EXAMPLE 3

This Example also illustrates a lotion which is suitable for topical application to the scalp.

The lotion has the following formulation:

	% w/w
D-Fucono-1,5-lactone	1.5
propan-2-ol	10
ethanol	88.5
perfume	q.s.

EXAMPLE 4

This Example also illustrates a hair tonic which is suitable for application to hair or scalp.

The hair tonic has the following formulation:

	% w/w
D-Glucaro-1,4-lactone	0.2
ethanol	40
water	59.80
perfume	q.s.

EXAMPLES 5 to 8

The following formulations represent lotions which can be used topically in the treatment of bald or balding male or female heads.

	% w/w			
	5	6	7	8
Hydroxyethyl cellulose	0.4	—	0.4	—
Absolute ethanol	25	25	25	25
Propane-1,2-diol	—	—	38.4	38.4
Butane-1,3-diol	38.4	38.8	—	—
Paramethyl benzoate	0.2	0.2	0.2	0.2
D-Glucaro-1,4:6,3-dilactone	5	—	—	—
L-Idaro-1,4-lactone	—	1	—	—
D-Glucurono-6,3-lactone	—	—	0.8	—
Galactaric acid lactone*	—	—	—	0.6
Perfume	1	1	1	1
Water to	100	100	100	100

*1,2,5-tri-O-acetyl-D-glucurono-6,3-lactone

EXAMPLES 9 to 12

The following formulations represent creams which can be used in the treatment of baldness.

	% w/w			
	9	10	11	12
Cetyl alcohol polyoxyethylene (10) stearic acids	4	4	4	4
Cetyl alcohol	4	4	4	4
Mineral oil	4	2	—	—
Paraffin wax	—	2	4	—
Partial glyceride of palmitic and stearic acids	—	—	—	4
N-Acetylglucosamine-lactone*	2	—	—	—
N-Acetylgalactosamino-lactone*	—	—	—	1
N-Acetylglucosamine	—	1.5	—	—
A-Acetylgalactosamine	—	—	2	—
Triethanolamine	0.75	0.75	0.75	0.75
Butane-1,3-diol	3	3	3	3
Xanthan gum	0.3	0.3	0.3	0.3
Preservative	0.4	0.4	0.4	0.4
Perfume	q.s.	q.s.	q.s.	q.s.
Water to	100	100	100	100

*2-Acetamido-2-deoxygluconolactone
*2-Acetamido-2-deoxygalactonolactone

EXAMPLE 13

This Example illustrates a water-in-oil high internal phase emulsion containing a glycosaminoglycanase inhibitor according to the invention.

The emulsion consisted of 10% by volume oily phase and 90% by weight aqueous phase.

The oily phase and the aqueous phase had the following constitution:

	% w/w
Oily phase	
Sorbitan monooleate	20
Quarternium-18 hectorite	5
Liquid paraffin	75
Aqueous phase	
D-Glucosamine-3-sulphate	0.5
Xanthan gum	1
Preservative	0.3
Perfume	q.s.
Sodium chloride (1% w/w solution) to	100

The emulsion was prepared by taking 10 parts by volume of the oily phase and to it adding slowly with stirring 90 parts by volume of the aqueous phase.

The high internal phase water-in-oil emulsion so formed can be applied topically to the scalp, to improve hair growth and regrowth.

The following examples 14 to 18 illustrate shampoos for use in washing the hair and scalp, and for promoting hair growth on the scalp.

EXAMPLE 14

	% w/w
Sodium lauryl ether sulphate (2 EO) [21% AD]	41.4
Lauryl dimethylamino acetic acid betaine: [30% AD]	4
Coconut fatty acid diethanolamine	1.5
Oleyl triethoxy phosphate (BRIPHOS 03D)	1
Polyglycol-polyamine condensation resin (POLYQUART H) [50% active]	1.5
Preservative, colouring matter, salt	0.58
2(S)-Carboxy-3(R),4(R),5(R)-trihydroxy piperidine	5
Perfume	q.s.
Water to	100

EXAMPLE 15

	% w/w
Sodium lauryl ether sulphate (2 EO) [100% AD]	12
POLYMER JR400	2.5
BRIPHOS 03D	2.5
D-Glucaro-1,4:6,3-dilactone	4
Magnesium Sulphate	5
Perfume	q.s.
Water to	100

EXAMPLE 16

	% w/w
Monoethanolamine lauryl sulphate: [100% AD]	20
JAGUAR C13S	3
BRIPHOS 03D	1.7
Coconut diethanolamide	5
D-Glucaro-1,4-lactone	1
Zinc gluconate	3
Perfume	q.s
Water to	100
pH adjusted to 6.5	

EXAMPLE 17

	% w/w
Sodium lauryl ether sulphate (3 EO): [100% AD]	12
JAGUAR C13S	0.3
BRIPHOS 03D	1
N-Acetylglucosamine	2
Sodium chloride	4
Perfume	q.s.
Water to	100
pH adjusted to 6.5	

EXAMPLE 18

	% w/w
Sodium lauryl ether sulphate (2 EO) [100% AD]	12
POLYMER JR400	3
BRIPHOS 03D	1
Opacifier	9
Magnesium sulphate	5
Perfume	q.s.
Water to	100
pH adjusted to 6.5	

EXAMPLES 19 to 24

The following Examples 19 to 24 illustrate powder compositions according to the invention which can be applied topically to the scalp.

	% w/w					
	19	20	21	22	23	24
Chemically modified starch	5	—	5	—	5	—
Chemically modified cellulose	—	5	—	5	—	5
Boric acid	10	10	10	10	10	10
Zinc oxide	5	5	5	5	5	5
D-Glucaro-1,4-lactone	3	2	5	1	—	—
Minoxidil glucuronide	5	10	2	4	3	5
D-Glucaro-1,4:6,3-dilactone	—	—	—	2	5	3
Perfume	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Chalk	10	10	10	10	10	10
Talc to	100	100	100	100	100	100

EXAMPLE 25

The following example illustrates a lotion according to the invention which can be applied topically to the scalp to prevent hair loss and stimulate hair regrowth.

	% w/w
D-Glucaro-1,4-lactone	7
Minoxidil	0.2
ethanol	16
citric acid	1.05
water to	100
pH adjusted to 4.2 with sodium hydroxide	

EXAMPLES 26 & 27

These examples illustrate hair tonics which are suitable for application to the hair and scalp.

The hair tonics had the following formulation:

	% w/w	
	26	27
Hydroxamic acid*	2	—
Hydroxamic acid⁻	—	3
ethanol	50	50
water	48	47
perfume	q.s.	q.s.

*HONHCOCH$_2$CH(n-Pentyl)COLeu-PheNH$_2$

⁻HONHCOCH$_2$CH(n-Pentyl)COLeu-AlaNH$_2$

EXAMPLE 28

This example illustrates a microgel which is suitable for topical application to hair or scalp.

The gel had the following formulation:

		% w/w
A.	Polyoxyethylene (10) oleyl ether	14.5
	Polyoxyethylene fatty glyceride	14.5
	Light liquid petroleum	13.7
	Propylene glycol	7.6
	Sorbitol	5.9
	Dilactone*	4
B.	Perfume	q.s.
C.	Water to	100

*2,5-Di-0-acetyl-D-glucaro-1,4:6,3-dilactone

This microgel was prepared by heating part A to 90° C. and part C to 95° and then adding part C to part A with stirring. Part B was then added at 70° C. and the final mixture cooled and poured into jars at 55° C. to 60° C. On further cooling, a gel was formed.

EXAMPLES 29 to 31

These examples illustrate shampoos which are suitable for topical application to hair in order to cleanse it, at the same time delivering chemical inhibitors to the scalp to enhance hair growth or regrowth.

The shampoo had the following formulation:

	29	30	31
Triethanolamine lauryl sulphate	16.8	18.0	16.8
Coconut diethanolamide	3.0	—	1.0
Hydroxypropylmethyl-cellulose[1]	0.25	0.1	0.3
Corn syrup (80% solids)[2]	20.5	40.0	21.0
Dimethylpolysiloxane[3]	1.0	1.0	—
Volatile silicone[4]	—	—	1.0
Cationic cellulose[5]	0.5	—	0.5
Ethyl alcohol (SDA 40)	9.0	10.0	10.0
Vinyl carboxy polymer[7]	0.75	0.3	0.75
D-Galactosamine	1	—	—
Glucuronic acid propyl ester	—	2	—
Iduronic acid methyl ester	—	—	5
Perfume, colour, preservative	q.s.	q.s.	q.s.
Water to	100	100	100
Acid or base to pH:	6.5	6.5	6.5

[1]Methocel E4M (Dow Chemical)
[2]42 Dextrose equivalent (Staley 1300)
[3]60,000 centistokes (Viscasil, GEC)
[4]Dow Corning 344
[5]Polymer JR 400
[6]Jaguar C-17
[7]Carbopol 941 (BF Goodrich)

EXAMPLES 32 to 35

The following formulations represent lotions which can be used topically in the treatment of bald or balding male or female heads.

	% w/w			
	32	33	34	35
Hydroxyethyl cellulose	0.4	—	0.4	—
Absolute ethanol	25	25	25	25
Propane-1,2-diol	—	—	38.4	38.4
Butane-1,3-diol	38.4	38.8	—	—
Paramethyl benzoate	0.2	0.2	0.2	0.2
N-Acetylmannosamine	5	—	—	—
Phosphorylated hesperidin	—	1	—	—
Sodium aurothiomalate	—	—	2	—
Substituted thiosemi-carbazone indoles	—	—	—	4
Perfume	1	1	1	1
Water to	100	100	100	100

EXAMPLE 36

This Example also illustrates a lotion which is suitable for topical application to the scalp.

The lotion has the following formulation:

	% w/w
Glucuronic acid	1.5
Diisopropyl sebacate	10
ethanol	88.5
perfume	q.s.

EXAMPLE 37

This Example also illustrates a hair tonic which is suitable for application to hair or scalp.

The hair tonic has the following formulation:

	% w/w
Glucurono-6,3-lactone	0.2
Pyroglutamic acid ethyl ester	10
ethanol	40
water	49.80
perfume	q.s.

I claim:

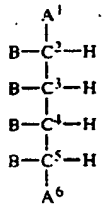
1. A method for inducing, maintaining or increasing hair growth in a mammal which comprises: applying a hair growth inducing, maintaining or increasing amount of a composition to the skin or hair, said composition comprising:

(i) a first chemical inhibitor selected from the group consisting of:

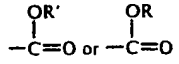
(a) a direct proteoglycanase inhibitor selected from the group consisting of:
1, 10-Phenanthroline
AcetylPhe-LeuSH
AcetylSer-LeuSH
AcetylTrp-LeuSH
AcetylPhe-Phe-LeuSH
$HSCH_2CH(i\text{-}Butyl)COPheNH_2$
$HSCH_2CH(i\text{-}Butyl)COLeu\text{-}PheNH_2$
AcetylTrp-IleSH
AcetylPhe-IleSH
$HOOCCH(i\text{-}Butyl)Leu\text{-}Leu\text{-}LeuOCH_3$
$HOOCCH(i\text{-}Butyl)Leu\text{-}Leu\text{-}AlaNH_2$
$HOOCCH(i\text{-}Butyl)Leu\text{-}Leu\text{-}PheNH_2$
$HOOCCH(i\text{-}Butyl)Leu\text{-}Leu\text{-}Leu\text{-}AlaNH_2$
$HONHCOCH_2CH(n\text{-}Pentyl)COLeu\text{-}PheNH_2$
$HONHCOCH_2CH(n\text{-}Pentyl)COLeu\text{-}AlaNH_2$
$HONHCOCH_2CH(i\text{-}Butyl)COLeu\text{-}PheNH_2$
$HONHCOCH_2CH(n\text{-}Pentyl)COVal\text{-}AlaNH_2$
and mixtures thereof;

(b) an indirect proteoglycanase inhibitor which is cationic oligomer;

(c) a glycosaminoglycanase inhibitor which is an at least one exoglycosidase inhibitor selected from the group consisting of aldonolactones and esterified aldonolactones of the formula:



where
A^1 and A^6 are —H, $—CH_3$, [-C=O]

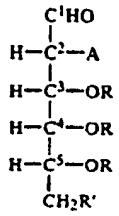


B is OR" or a lactone linkage to position 1 or 6, or $-NHCOCH_3$ and where R is —H or C_2 to C_8 alkyl,

R' is the remainder of the molecule joined through another C atom at positions 2 to 5 to form a lactone,

R'' is —H or C_2 to C_4 acyl of either configuration with respect to the backbone of this molecule;

(d) a glycosaminoglycanase inhibitor which is an exoglycosidase inhibitor selected from the group consisting of monosaccharides and esterified monosaccharaides of the formula:



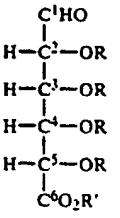
where
A is —OR or —$NHCOCH_3$,
R is —H, —SO_3M, C_2 to C_4 acyl,
R' is —H or —OR,
M is —H or a metal cation;

(e) a glycosaminoglycanase inhibitor which is an endoglycosidase inhibitor selected from the group consisting of:
phosphorylated hesperidin
sodium aurothlomalate
substituted thiosemicarbazone indoles, and
mixtures thereof;

(f) a glycosaminoglycanase inhibitor which is a sulphatase or sulphamatase inhibitor selected from water soluble salts having an anion selected from the group consisting of:
inorganic sulphate
sulphite
pyrophosphate
fluoride
borate
chloride
gluconate, and
mixtures thereof;

(g) a glycosaminoglycanase inhibitor which is the sulphatase inhibitor D-Glucosamine-3-sulphate; and

(h) a glycosaminoglycan chain uptake inhibitor selected from the group consisting of hexuronic acids or esters thereof of the formula:



where
R is —H, —SO_3M, C_2 to C_4 acyl,
R' is —H or C_2 to C_8 alkyl; and

(ii) a cosmetically acceptable vehicle for the chemical inhibitor; provided that when the first chemical inhibitor is a weak inhibitor, such that a 1mM aqueous solution of the inhibitor reduces proteoglycanase activity, glycosaminoglycan activity or cellular uptake of glycosaminoglycan chains, by from 5 to 50%, in accordance with at least one of the assay tests as herein described, then there is also present in the composition at least one of, a second chemical inhibitor selected from the group consisting of proteoglycanase inhibitors, glycosaminoglycanase inhibitors, glycosaminoglycan chain cellular uptake inhibitors or mixtures thereof, an activity enhancer; the total amount of chemical inhibitor present in the composition being sufficient to increase hair growth in a rat, when said composition is applied topically thereto, by at least 10% more than that obtainable using an equal amount of a control composition from which the said inhibitors have been omitted.

2. A method according to claim 1, in which the inhibitor is a cationic oligomer indirect proteoglycanase inhibitor selected from the group consisting of:
Arq-Arq-Arq,
Cys-Arq-Arq-Arq-Lys-Arq-Arq,
Pro-Arq-Arq-Arq-Arq,
Arq-Pro-Val-Arq-Arq-Arq-Arq-Arq-Pro-Val, and mixtures thereof.

3. A method according to claim 1 wherein the inhibitor is an aldonolactone exoglycosidase inhibitor selected from the group consisting of:
L-Galactonic acid-lactone
L-Arabino-1, 5-lactone
D-Fucono-1, 5-lactone
D-Glucaro-1, 4-lacone
D-Glucurono-6, 3-lactone
Galactaric acid lactone
2-Acetamido-2-deoxygluconolactone
2-Acetamido-2-deoxygalactonolactone
D-Glucaro-1,4:6,3-dilactone
L-Idaro-1,4-lactone, and
mixture thereof.

4. A method according to claim 1 in which the inhibitor is an exoglycosidase inhibitor which is an esterified aldonolactone selected from the group consisting of:
2, 3, 5, -Tri-O-acetyl-D-glucaro-1,4-lactone, 2,5-Di-o-acetyl-D-glucaro-1, 4:6, 3-dilactone and mixtures thereof.

5. A method according to claim 1 in which the inhibitor is a monosaccharide or esterified monosaccharide exoglycosidase inhibitor selected from the group consisting of:
N-Acetylglycosamine,
N-Acetylgalactosamine,
D-Galactosamine, and
mixtures thereof.

6. A method according to claim 1 in which the inhibitor is a sulphatase inhibitor selected from the group consisting of the anions:
inorganic sulphate,
sulphite,
pyrophosphate,
fluoride
borate
chloride
gluconate, and mixtures thereof,
each anion being in the form of a water-soluble metal or ammonium salt.

7. A method according to claim 6 in which the salt is selected from the group consisting of magnesium sulphate and zinc gluconate.

8. A method according to claim 7, in which the salt is magnesium sulphate.

9. A method according to claim 6 in which the sulphamase inhibitor is selected from the group consisting of the anions:

inorganic sulphate
sulphite
pyrophosphate
fluoride
borate, and
mixtures thereof,
each anion being in the form of a water-soluble metal or ammonia salt.

10. A method according to claim **1**, in which the inhibitor is a hexuronic acid glycosaminoglycan chain uptake inhibitor selected from the group consisting of glucuronic acid, iduronic acid and mixtures thereof.

11. A method according to claim **1**, in which the total amount of chemical inhibitor is sufficient to increase hair growth in a rat, when the composition is applied topically thereto, by 20% to 50% more than that obtainable using the same amount of a control composition from which said inhibitors have been omitted.

12. A method according to claim **1**, in which the total amount of chemical inhibitor in the composition, is sufficient to increase their growth in a rat, when said composition is applied topically thereto, by at least 50% more than that obtained using the same amount of a control composition from which said inhibitors have been omitted.

13. A method according to claim **1**, in which the amount of the chemical inhibitor in the composition comprises from 0.0001 to 99% by weight of the composition.

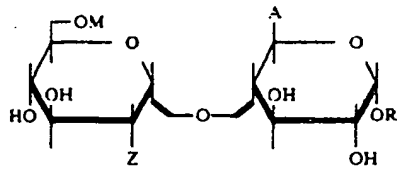
14. A method according to claim **13**, in which the amount of chemical inhibitor comprises from 0.1 to 20% by weight of the composition.

15. A method according to claim **1** in which the composition additionally comprises from 0.01 to 10% by weight of a perfume.

16. A method according to claim **1** in which the composition additionally comprises an activity enhancer.

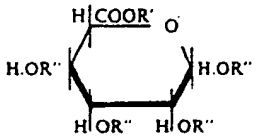
17. A method according to claim **16**, in which the activity enhancer comprises at least one hair growth stimulant selected from the group consisting of:
Benzalkonium chloride
Benzethonium chloride
Phenol
Estradiol
Diphenhydramine hydrocholoride
Chlorpheniramine maleate
Chlorophyllin derivatives
Cholesterol
Salicylic acid
Cystine
Red pepper tincture
Benzyl nicotinate
dl-Menthol
Peppermint oil
Calcium pantothenate
Panthenol
Castor oil
Hinokitiol
Prednisolone
Resorcinol, and
mixtures thereof.

18. A method according to claim **16**, in which the activity enhancer is a hair growth stimulant selected from the group consisting of α-1,4 esterified dissaccharides of the formula:

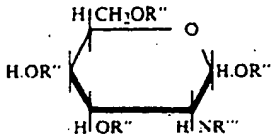


where
Z represents a functional nitrogen group selected from an azide group or a group having the structure -NHB, in which B represents —H an acetyl group or sulphate as a salt with an organic or inorganic cation; M represents —H or SO_3m_1, or acetyl group, and M_1 is an organic or metallic cation, or an acetyl group, and;
R represents a C_1 to C_4 alkyl radical, or an aryl radical;
A represents a functional group selected from a carboxylic acid group of —$COOR_1$, where R_1 represents —H a C_1 to C_4 alkyl radical or a metal.

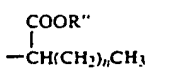
19. A method according to claim **16**, in which the activity enhancer is a hair growth stimulant selected from the group consisting of esterified oligosaccharides, including at least one esterified disaccharide unit consisting of a uronic acid residue of the formula:



and a hexosamine residue of the formula:



where
R' is —H, C_3 to C_{10} alkyl or



R" is —H, C_1 to C_4 alkyl, —$CO(CH_2)_mCH_3$, —SO_3M,
R"' is —H, —$CO(CH_2)_mCH_3$, or —SO_3M,
M is —H, or a metallic or organic cation
n is 0 or an integer of from 1 to 7, and
m is 0 or the integer 1 or 2;
the groups designated R" being the same or different, one R" group from each pyranose ring structure being linked by a glycosidic linkage having the configuration α-1,3, α-1,4, β-1,3 or β-1,4; and the —COOR'. —CH_2OR" and —OR" groups being of either configuration with respect to the pyranose rings.

20. A method according to claim **16**, in which the activity enhancer is a hair growth stimulant selected from the group consisting of:
minoxidil glucuronides,
minoxidil sulphates, and

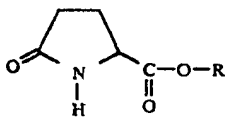
mixtures thereof.

21. A method according to claim 16, in which the activity enhancer is a penetration enhancer.

22. A method according to claim 21, which the penetration enhancer is selected from the group consisting of:

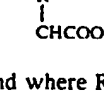
Dioctyl adipate
Dicapryl adipate
Diisopropyl adipate
Diisopropyl sebacate
Dibutyl sebacate
Diethyl sebacate
Dimethyl sebacate
Dioctyl sebacate
Dibutyl suberate
Dioctyl azelate
Debenzyl sebacate
Dibutyl phthalate
Dibutyl acelate
Ethyl myristate
Dimethyl azelate
Butyl myristate
Dibutyl succinate
Didecyl phthalate
Decyl oleate
Ethyl caproate
Ethyl salicylate
Isopropyl palmitate
Ethyl laurate
2-ethyl-hexyl pelargonate
Isopropyl isostearate
Butyl laurate
Benzyl benzoate
Butyl benzoate
Hexyl Laurate
Ethyl caprate
Ethyl caprylate
Butyl stearate
Benzyl salicylate
2-hydroxypropanoic acid
2-hydroxyoctanoic acid, and mixtures thereof.

23. A method according to claim 21, in which the penetration enhancer is selected from the group consisting of esters of pyroglutamic acid having the structure:



(1)

where R is C_1 to C_{30} alkyl, or



and where R′ and R″ are the same or different and are each represented by H or the grouping:

$$[(CH_3)_u\text{-}(CH_2OH)_v\text{-}(CH_2)_w\text{-}(CH_3CH_2)_x\text{-}(CH{=}CH)_z]\text{-} \quad (2)$$

where
u is zero or 1
v is zero, or the integer 1 or 2,
w is zero, or an integer of from 1 to 21
x is zero, or an integer of from 1 to 4,
y is zero, or the integer 1 or 2,
z is zero, or an integer of from 1 to 22, and
u+v+w+x+y+z is an integer of from 1 to 22;
provided that when the subgrouping (CH+CH) is present, then the total number of carbon atoms in said grouping is from 10 to 22.

24. A method according to claim 23, in which the ester of pyroglutamic acid is selected from the group consisting of:

pyroglutamic acid methyl ester
pyroglutamic acid ethyl ester
pyroglutamic acid n-propyl ester
pyroglutamic acid n-butyl ester
pyroglutamic acid n-heptyl ester
pyroglutamic acid n-octyl ester
pyroglutamic acid n-nonyl ester
pyroglutamic acid n-decyl ester
pyroglutamic acid n-undecyl ester
pyroglutamic acid n-dodecyl ester
pyroglutamic acid n-tridecyl ester
pyroglutamic acid n-tetradcyl ester
pyroglutamic acid n-hexadecyl ester
pyroglutamic acid n-octadecyl ester
pyroglutamic acid n-eicosyl ester
pyroglutamic acid iso-propyl ester
pyroglutamic acid 2-methylhexyl ester
pyroglutamic acid 2-ethylhexyl ester
pyroglutamic acid 3,7-dimethyloctyl ester
pyroglutamic acid 2-hexyldecyl ester
pyroglutamic acid 2-octyldodecyl ester
pyroglutamic acid 2,4,4-trimetyl-1-pentane ester
pyroglutamic acid methyloctyl ester, and mixtures thereof.

25. A method according to claim 23, in which the ester of pyroglutamic acid is selected from the group consisting of:

2-[pyroglutamoyloxy]-propionic acid
methyl-2-[pyroglutamoyloxy]-acetate
ethyl-2-[pyroglutamoyloxy]-n-propionate
ethyl-2-[pyroglutamoyloxy]-n-butyrate
ethyl-2-[pyroglutamoyloxy]-iso-butyrate
ethyl-2-[pyroglutamoyloxy]-n-valerate
ethyl-2-[pyroglutamoyloxy]-n-caproate
ethyl-2-[pyroglutamoyloxy]-n-heptylate
ethyl-2-[pyroglutamoyloxy]-n-caprylate
ethyl-2-[pyroglutamoyloxy]-n-pelargonate
ethyl-2-[pyroglutamoyloxy]-3-hydroxybutyrate
iso-propyl-2-[pyroglutamoyloxy]-n-propionate
iso-propyl-2-[pyroglutamoyloxy]-n-caprylate
n-propyl-2-[pyroglutamoyloxy]-n-propionate
n-propyl-2-[pyroglutamoyloxy]-n-caprylate
stearyl-2-[pyroglutamoyloxy]-n-propionate
12-hydroxystearyl-2-[pyroglutamoyloxy]-n-propionate
stearyl-2-[pyroglutamoyloxy]-n-stearate
palmityl-1-2-[pyroglutamoyloxy]-n-propionate
linoleyl-2-[pyroglutamoyloxy]-n-propionate
linoleyl-2-[pyroglutamoyloxy]-n-caprylate
lauryl-2-[pyroglutamoyloxy]-n-caprylate
stearyl-2-[pyroglutamoyloxy]-n-caprylate
glyceryl mono(2-[pyroglutamoyloxy]-n-propionate)
glyceryl mono(2-[pyroglutamoyloxy]-n-caprylate)
glyceryl di(2-[pyroglutamoyloxy]-n-propionate), and mixtures thereof.

26. A method according to claim 21, in which the penetration enhancer is selected from the group consisting of:

Dimethyl sulphoxide

N,N-Dimethyl acetamide
N.N-Dimethyl formamide
2-Pyrrolidonel-Methyl-2-pyrrolidone
5-Methyl-2-pyrrolidone
1,5-Dimethyl-2-pyrrolidone
1-Ethyl-2-pyrrolidone
Phosphine oxides
Sugar esters
Tetrahydrofurfural alcohol
Urea
Diethyl-m-toluamide
1-Dodecylazacyloheptan-2-one, and mixtures thereof.

27. A method according to claim 21, in which the penetration enhancer comprises an anionic surface active agent selected from the group consisting of:
metallic or alkanolamine salts of fatty acids
alkyl benzene sulfonates
alkyl sulphates
alkyl ether sulphates
sulphosuccinates
monoglyceride sulphates
isethionates
methyl taurides
acyl sarcosinates
acyl peptides
acyl lactylates
polyalkoxylated ether glycollates
phosphates, and mixtures thereof.

28. A method according to claim 21, in which the penetration enhancer comprises an amphoteric surface active agent selected from the group consisting of:
imidazol compounds
N-alkylamino acids
betaines, and
mixtures thereof

29. A method according to claim 21, in which the penetration enhancer comprises a nonionic surface active agent selected from the group consisting of:
fatty acid alkanolamides
esters of polyalcohols
polyglycerol esters
polyalkoxylated compounds
ethers
ester ethers
amine oxides, and
mixtures thereof.

30. A method of claim 1 wherein the composition is in the form of a lotion, cream, shampoo or hair conditioner.

31. A method of claim 1 wherein the mammal is a human being.

* * * * *

US005192534A

United States Patent [19]

Grollier et al.

[11] Patent Number: 5,192,534

[45] Date of Patent: Mar. 9, 1993

[54] **COMPOSITION FOR INDUCING AND STIMULATING HAIR GROWTH AND/OR RETARDING ITS LOSS, BASED ON PYRIMIDINE DERIVATIVES AND SUNSCREENS**

[75] Inventors: **Jean F. Grollier; Isabelle Richoux,** both of Paris, France

[73] Assignee: **L'Oreal, Paris, France**

[21] Appl. No.: **834,977**

[22] Filed: **Feb. 13, 1992**

Related U.S. Application Data

[63] Continuation of Ser. No. 459,128, Dec. 29, 1989, abandoned.

[30] **Foreign Application Priority Data**

Dec. 30, 1988 [FR] France 88 17466

[51] Int. Cl.[5] A61K 7/42

[52] U.S. Cl. 424/59; 424/60; 514/256

[58] Field of Search 424/60, 59; 514/256

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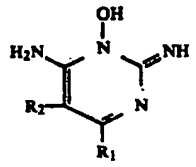
Primary Examiner—Thurman K. Page
Assistant Examiner—William E. Benston, Jr.
Attorney, Agent, or Firm—Jacobson, Price, Holman & Stern

[57] **ABSTRACT**

The invention relates to a composition intended for inducing and stimulating hair growth and decreasing its loss, containing, in a physiologically acceptable medium, at least one pyrimidine derivative corresponding to the formula:



(I)

in which R_1 denotes

where R_3 and R_4 are hydrogen, lower cycloalkyl, alkyl, alkenyl or alkylaryl, it also being possible for R_3 and R_4, with the nitrogen atom to which they are attached, to form a heterocycle, preferably piperidyl, and R_2 is preferably hydrogen, as well as its addition salts with physiologically acceptable acids; and at least one agent screening out UV radiation, selected from 2-hydroxy-4-methoxybenzophenone, 2-ethylhexyl para-dimethylaminobenzoate, pentyl para-dimethylaminobenzoate, 2-ethylhexylpara-methoxycinnamate, 4-(1,1-dimethylethyl)-4'-methoxydibenzoylmethane, N-(2-ethylhexyl)-3-[(3'-methoxy-4'-n-butoxy)benzylidene]-10-camphorsulphonamide, 3-(4-methylbenzylidene)camphor, homomenthyl salicylate, 2-ethylhexyl salicylate, para-aminobenzoic acid and 2-hydroxy-4-methoxybenzophenone-5-sulphonic acid, as well as mixtures thereof.

31 Claims, No Drawings

COMPOSITION FOR INDUCING AND STIMULATING HAIR GROWTH AND/OR RETARDING ITS LOSS, BASED ON PYRIMIDINE DERIVATIVES AND SUNSCREENS

This application is a continuation of application Ser. No. 459,128, filed Dec. 29, 1989, now abandoned.

The invention relates to new compositions for inducing and stimulating hair growth and/or retarding its loss, containing, in combination, pyrimidine derivatives and at least some agents screening out UV radiation.

Compositions enabling alopecia to be abolished and reduced and, in particular, hair growth to be induced and stimulated and/or its loss to be decreased have been sought for many years in the cosmetics or pharmaceutical industry.

Alopecia, as is well known, is due, in particular, to a disturbance of the hair cycle, inasmuch as it is generally found to occur when the growth phase known as the "anagen phase" is shortened, as a result of which transition of hairs to the telogen phase occurs earlier and the hairs fall in larger numbers.

Successive growth cycles result in increasingly finer and increasingly shorter hairs, gradually converting to an unpigmented down which can lead to baldness.

The changes in these different categories of hair may be determined by means of a trichogram, and especially a phototrichogram.

In this connection, compounds such as 6-amino-1,2-dihydro-1-hydroxy-2-imino-4-piperidinopyrimidine and its derivatives have already been proposed. Such compounds are described, more especially, in U.S. Pat. No. 4,139,619.

In Application WO-A-83/02,558, compositions based on retinoids and minoxodil, used, in particular, for stimulating human hair growth and treating some types of alopecia, have also been described.

It was, however, found that 6-amino-1,2-dihydro-1-hydroxy-2-imino-4-piperidinopyrimidine, also known by the name of minoxidil, displayed problems of solubilization, as a result of which lotions recommended for topical application to the scalp generally contained this compound in the solubilized state only at relatively low concentrations.

Means have hence been sought which are capable of advantageously modifying the solubility of these pyrimidine derivatives, both to permit more rapid dissolution of the active substance and to prevent recrystallization of the latter in the course of time, in particular crystallization of minoxidil on the scalp brought about by evaporation of the solvent, thereby leading to a loss of active substance through a phenomenon of powdering, the cosmetic effect of which is, in addition, undesirable, or to permit the use of concentrated solutions of minoxidil which can be diluted at the time of use with other compositions containing active substances.

Moreover, and inasmuch as these compositions are intended for topical application to the scalp and this application is generally not followed by a rinsing step, it has proved essential to perform the solubilization of the active substance with cosolubilizing agents whose effects on the hair of the treated individuals are cosmetic, that is to say they do not lead to the hair becoming gummy, sticky or greasy.

Agents screening out UV radiation, generally used for the protection of the human epidermis, in particular for preserving the skin from the adverse effects of ultraviolet radiation, have, moreover, been known for a long time.

The Applicant discovered, and this forms the subject of the invention, that, surprisingly, some agents screening out UV radiation, protecting the scalp of alopecic subjects which is directly exposed to the possibly adverse effects of UV radiation, also enabled, in the case of some of these agents, improved solubilization of the pyrimidine derivatives to be obtained.

This effect is especially surprising when it is realized that the sunscreen properties are completely unrelated to the cosolubilization properties of these sunscreen agents.

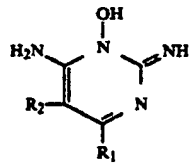
A subject of the invention hence consists of a combination of pyrimidine derivatives and certain agents screening out UV radiation, in a composition intended for inducing and stimulating hair growth and decreasing its loss.

Another subject of the invention consists of cosmetic and/or pharmaceutical compositions containing such a combination.

A subject of the invention also consists of treatment processes employing such a combination, as well as devices for the use of the combination.

Other subjects of the invention will become apparent on reading the description and the examples which follow.

The composition intended for inducing or stimulating hair growth and decreasing its loss, according to the invention, is essentially characterized in that it contains, in a physiologically acceptable medium, at least one pyrimidine derivative corresponding to the formula:



(I)

in which R_1 denotes a group

in which R_3 and R_4 may be selected from hydrogen and a lower cycloalkyl, alkyl, alkenyl or alkylaryl group, it also being possible for R_3 and R_4, with the nitrogen atom to which they are attached, to form a heterocycle selected, inter alia, from aziridinyl, azetidinyl, pyrrolidinyl, piperidyl, hexahydroazepinyl, heptamethylenimine, octamethylenimine, morpholine and 4-(lower alkyl)piperazinyl groups, it being possible for the heterocyclic groups to be substituted on the carbon atoms with one to three lower alkyl, hydroxy or alkoxy groups; and the group R_2 is selected from hydrogen and a lower haloarylalkyl, alkyl, alkenyl, alkylalkoxy, cycloalkyl, aryl, alkylaryl, arylalkyl, alkylarylalkyl or alkoxyarylalkyl group; as well as the addition salts with physiologically acceptable acids;

and at least one agent screening out UV radiation, selected from the following compounds:

2-hydroxy-4-methoxybenzophenone;

2-ethylhexyl para-dimethylaminobenzoate;
pentyl para-dimethylaminobenzoate;
2-ethylhexyl para-methoxycinnamate;
4-(1,1-dimethylethyl)-4'-methoxydibenzoylmethane;
N-(2-ethylhexyl)-3-[(3'-methoxy-4'-n-butoxy)benzylidene]-10-camphorsulphonamide;
3-(4-methylbenzylidene)camphor;
homomenthyl salicylate;
2-ethylhexyl salicylate;
para-aminobenzoic acid; and
2-hydroxy-4-methoxybenzophenone-5-sulphonic acid;
as well as mixtures thereof.

In the formula (I), the alkyl or alkoxy groups preferably denote a group having 1 to 4 carbon atoms; alkenyl preferably denotes a group having 2 to 5 carbon atoms; aryl preferably denotes phenyl; the cycloalkyl group preferably denotes a group having between 4 and 6 carbon atoms; halogen preferably denotes chlorine or bromine.

More especially preferred compounds of formula (I) are selected from the compounds in which R_2 denotes hydrogen and R_1 denotes a group:

in which R_3 and R_4 form a piperidyl ring, as well as their salts such as, for example, the sulphate. The especially preferred compound consists of 6-amino-1,2-hydro-1-hydroxy-2-imino-4-piperidinopyrimidine, also known as "minoxidil".

The pyrimidine derivatives of formula (I) are used according to the invention in proportions preferably of between 0.1 and 10% by weight, and more especially between 1 and 5% by weight, relative to the total weight of the composition.

The agents screening out UV radiation, defined above, are preferably present in proportions sufficient to increase the solubility of the pyrimidine derivative of formula (I) in the medium in question, this increase preferably being greater than 10%, and especially greater than 20%, relative to the solubility of the pyrimidine derivative of formula (I) in this medium.

The agents screening out UV solar radiation are preferably used in proportions of between 0.1 and 10%, and preferably between 0.3 and 4%, relative to the total weight of the composition.

The compositions according to the invention may be aqueous or alternatively anhydrous, the aqueous or anhydrous medium being physiologically acceptable.

Aqueous medium denotes a medium consisting of water or a mixture of water and a physiologically acceptable solvent.

Anhydrous medium, according to the invention, denotes a solvent medium containing less than 1% of water. This anhydrous medium can consist of a solvent or mixture of solvents selected, more especially, from C_2–C_4 lower alcohols such as ethyl alcohol, alkylene glycols such as propylene glycol, and alkylene glycol or dialkylene glycol alkyl ethers, the alkyl or alkylene radicals being radicals having 1 to 4 carbon atoms.

These same solvents, in particular ethyl alcohol, may be used in the aqueous medium.

The compositions according to the invention can also contain different adjuvants customarily used in compositions intended for topical application in cosmetics or pharmacy, including preservatives, colourings and fragrances.

These compositions can also contain thickening agents well known in the prior art.

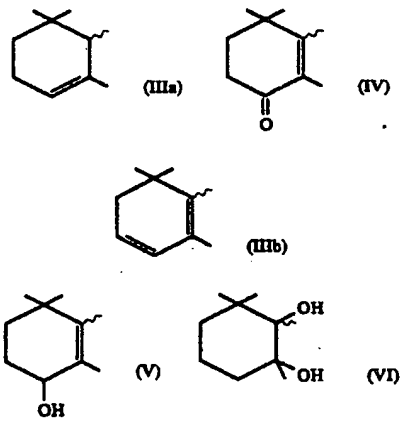
An especially advantageous embodiment of the invention consists in using, in addition to the pyrimidine derivative and the sunscreen agent, at least one retinoid which can either be used in combination in the same composition or in a mixture with the composition defined above at the time of use, or be used in a sequential application before or after application of the composition containing the pyrimidine derivative and the sunscreen agent, successively or separated by an interval of time.

The retinoids are, in particular, selected from the compounds corresponding to the formula:


(II)

in which:

a) A is a group selected from the groups of formulae:


(IIIa) (IV) (IIIb) (V) (VI)

in which:

when A denotes a group of formula (IIIa), R is selected from the following groups:

CHO; CH_2OR_5,

in which R_5 denotes hydrogen or C_1–C_4 lower alkyl;

a group

where R_6 denotes C_1–C_{16} linear or branched alkyl; CH_2SR_7, in which R_7 denotes hydrogen or methyl;

in which X denotes:

(i) OH;

(ii) OR_6, where R_8 denotes a C_1–C_{15} alkyl radical, C_1–C_4 arylalkyl radical optionally substituted on the aryl group, C_1–C_4 arylcarboxyalkyl radical

optionally substituted on the aryl group, or C_1–C_4 hydroxyalkyl or C_1–C_4 amidoalkyl radical;

(iii) NR_9R_{10}, in which R_9 and R_{10}, which may be identical or different, denote hydrogen, C_1–C_6 alkyl, C_1–C_4 hydroxyalkyl or optionally substituted aryl;

it being possible for R_9 or R_{10} to represent an optionally substituted heterocycle or, together with the nitrogen atom to which they are attached, to form a heterocycle which is itself optionally substituted;

(iv) an N_3 group;

or alternatively a group of formula CH_2NHR_{11}, in which R_{11} denotes an optionally substituted benzoyl radical;

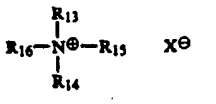
when A denotes a group of formula (IIIb), (IV), (V) or (VI), R_1 denotes COOH as well as its salified or esterified form;

b) A is a group selected from aryl or substituted aryl groups, a heterocycle or substituted heterocycle, an aryl-heterocyclic group optionally substituted on the heterocycle or an aryl-homocyclic group optionally substituted on the aromatic ring, R in this case denoting a COOH group, a group $COOR_{12}$ where R_{12} denotes a C_1–C_4 alkyl radical or alternatively an amide group substituted with a C_1–C_4 alkyl group, as well as their physiologically acceptable salts and esters.

In the abovementioned formula, C_1–C_4 alkyl preferably denotes methyl, ethyl, n-butyl or t-butyl; C_1–C_{16} alkyl preferably denotes ethyl, propyl or palmityl; aryl preferably denotes phenyl or benzyl, and the substituents on the aryl groups are preferably C_1–C_4 alkyl, C_1–C_{12} alkoxy, hydroxyl, halogen or nitro groups, it being possible for the alkoxy or alkyl groups themselves to be optionally substituted with an OH group.

The heterocyclic groups may be selected, inter alia, from groups derived from phthalimide, from succinimide and from 4- to 6-membered heterocycles containing one or more oxygen atoms, one or more nitrogen atoms.

The compounds of the retinoid family, defined above, are, in particular, selected from: retinal, retinol, retinyl acetate, propionate and palmitate, retinoic acid in all-trans, 13-cis, 9-cis, 11-cis, 9,13-dicis and 11,13-dicis forms, the corresponding zinc retinoates and the quaternary ammonium retinoates of formula:



(VII)

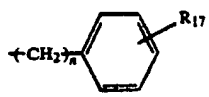
in which

$X^{\ominus}$ denotes an all-trans- or 13-cis-retinoate radical; and

(i) R_{13}, R_{14} and R_{15}, which may be identical or different, denote a C_1–C_4 linear alkyl group which can bear one or more hydroxyl group(s) in the chain,

R_{16} denoting C_{12}–C_{18} linear alkenyl or alkyl;

(ii) R_{15} denotes a group:



in which:

n is equal to 0 or 1,

R_{17} represents a hydrogen or halogen atom or a hydroxyl,

C_1–C_{18} alkyl or hydroxyalkyl or C_2–C_{18} acyl group;

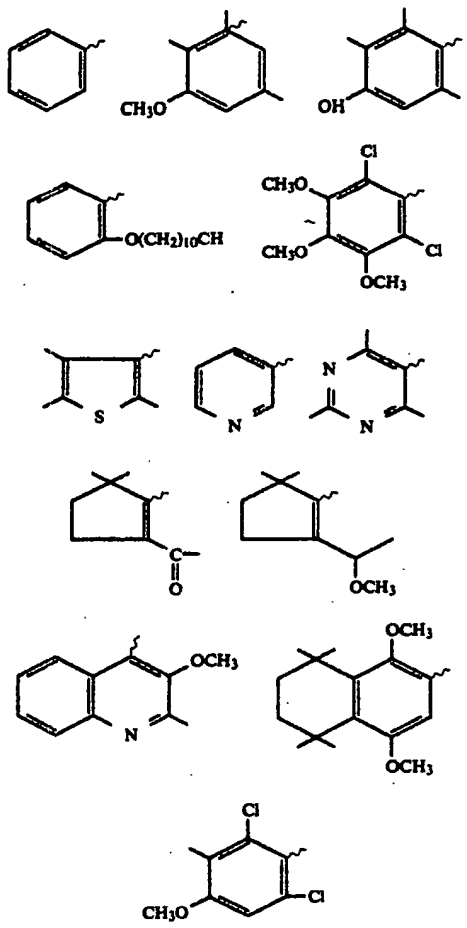
R_{13}, R_{14} and R_{15} having the meanings stated under (i);

(iii) R_{13} and R_{14} can form an aliphatic heterocycle containing at least one oxygen atom, one nitrogen atom or one sulphur atom;

R_{15} or R_{16} having the meanings stated under (i) and (ii).

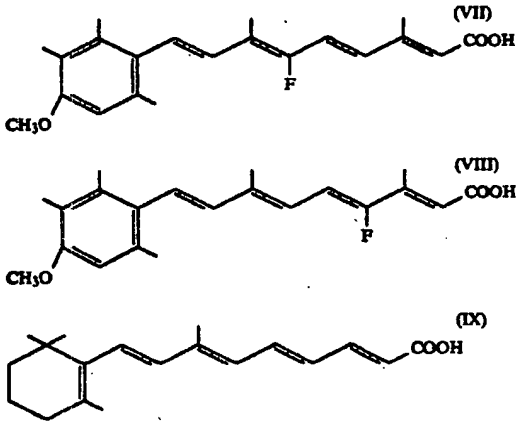
Other compounds falling within the definition of retinoids which are especially usable according to the invention are selected from: all-trans-retinoyloxyacetamide, a mixture of 2-hydroxy-1-propyl and 1-hydroxy-2-propyl all-trans-retinoates, 2-hydroxyethyl all-trans-retinoate, 4-nitrobenzyl all-trans-retinoate, benzyl all-trans-retinoate, 4-(all-trans-retinoyloxyacetyl)catechol, 2-cyclohexylethyl all-trans-retinoate, 10-carboxymethyldecyl all-trans-retinoate, 4-hydroxybutyl all-trans-retinoate, cholesteryl all-trans-retinoate, 4-bromobenzyl all-trans-retinoate, cholesteryl all-trans-retinoyloxyacetate, all-trans-retinoyloxyacetylbenzene, 4-(all-trans-retinoyloxyacetyl)bromobenzene, 4-(all-trans-retinoyloxyacetyl)nitrobenzene, 4-(all-trans-retinoyloxyacetyl)benzonitrile, all-trans-retinoyloxyacetyl-2,4-dichlorobenzene, N-(all-trans-retinoyloxy)phthalimide, N-(all-trans-retinoyloxy)succinimide, 4-(all-trans-retinoyloxyacetyl)methoxybenzene, 4-(all-trans-retinoyloxyacetyl)phenol, 4-(all-trans-retinoyloxyacetyl)-3,4,5-trimethoxybenzene, 4-(all-trans-retinoyloxyacetyl)-2,4,6-trimethylbenzene, 4-(all-trans-retinoyloxyacetyl)toluene, 4-(all-trans-retinoyloxyacetyl)ethoxybenzene, 4-(all-trans-retinoyloxyacetyl-)acetoxybenzene, 4-(all-trans-retinoyloxyacetyl)naphthalene, 4-(all-trans-retinoyloxyacetyl)biphenyl, 4-(all-trans-retinoyloxyacetyl)-2,5-dimethoxybenzene, 1-(all-trans-retinoyloxyacetyl)-2,4-dimethylbenzene, 1-(all-trans-retinoyloxyacetyl)-3,4-diacetoxybenzene, all-trans-retinamide, 2-hydroxyethyl all-trans-retinamide, N-ethyl-all-trans-retinamide, 4-(all-trans-retinoyl-)aminophenol, N-(methyldimethyldioxolane)-retinamide, N-(ortho-carboxyphenyl)retinamide, N-(p-carboxyphenyl)retinamide, N-hydroxypropyl-all-trans-retinamide, N-(hydroxypropyl)-13-cis-retinamide, N-(5-tetrazolyl)-all-trans-retinamide, N-(5-tetrazolyl)-13-cis-retinamide, N-(3,4 methylenedioxyphenylmethyl)-all-trans-retinamide, N-(n-propyl)-all-trans-retinamide, N-tert-butyl-all-trans-retinamide, N-(1,1,3,3-tetramethylbutyl)-all-trans-retinamide, N-(4-carboxymethyl-3-hydroxyphenyl)-all-trans-retinamide, N-[β-(3,4-dimethoxyphenyl)ethyl]-all-trans-retinamide, 2-(all-trans-retinoylamino)benzotriazole, 1-(all-trans-retinoyl)-1,2,4-triazole, N-(all-trans-retinoyl)imidazole, 1-nicotinoyl-2-(all-trans-retinoyl)hydrazine, N-(all-trans-retinoyl)morpholine, trans-β-ionone (all-trans-retinoyl)hydrazone, N,N'-dicyclohexyl-N-(all-trans-retinoyl)urea, acetone (all-trans-retinoyl)hydrazone, N-benzoylretinylamine and retinoyl azide.

The groups represented by A and defined above in paragraph (b) in connection with the aryl, substituted aryl, heterocyclic or substituted heterocyclic groups, aryl-heterocyclic groups substituted on the heterocyclic or aryl-homocyclic groups substituted on the aromatic ring are, in particular, selected from the following groups:



The group R can have the meanings COOH, $CONHC_2H_5$, $COOC_2H_5$.

Especially preferred compounds in this family are motretinide and etretinate. Other retinoids which are usable according to the invention correspond to the following formulae or their physiologically acceptable salts or esters.



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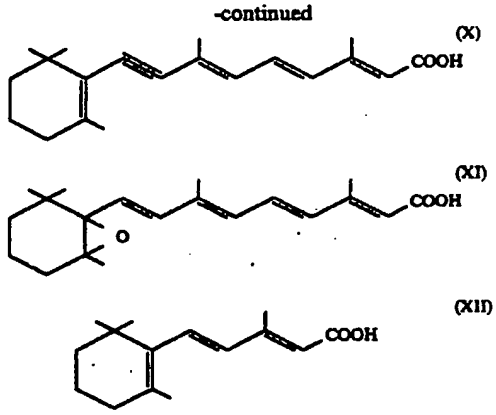
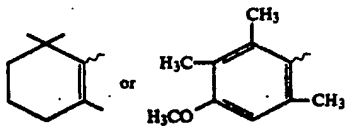


The compounds of the retinoid family which are usable according to the invention are, in particular, described in U.S. Pat. Nos. 4,190,594 and 4,126,698, EP-A-010,209, EP-A-010,208, EP-A-09,776, French Patent 2,293,193 and EP-A-033,095, or in Cancer Research 40,3413-3425, October 1980 or in Annals of the New York Academy of Sciences, Vol. 359.

Especially preferred retinoids are those corresponding to the general formula (II) shown above in which R_1 denotes a radical

in which X denotes OH or OY, Y denoting an alkyl group having from 1 to 15 carbon atoms, it also being possible for X to denote an amino group optionally mono- or disubstituted with a lower alkyl group preferably having 1 to 6 carbon atoms, it also being possible for R to denote a —CH_2OH or —CHO group, and A denoting a group:



these compounds preferably being in the form of the all-trans or 13-cis isomers.

Among especially preferred derivatives, there may be mentioned the products commonly designated tretinoin, isotretinoin, retinol, motretinide and etretinate, retinol derivatives such as the acetate, palmitate or propionate and zinc all-trans-retinoate, and still more especially tretinoin or all-trans retinoic acid.

The retinoids used according to the invention can be present in the same composition as the pyrimidine derivative and sunscreen agent, and preferably in proportions of between 0.001 and 2% by weight, and especially between 0.01 and 0.5% by weight, relative to the total weight of the composition.

Another form of the invention can consist of a combination comprising a component (A) consisting of the composition based on the pyrimidine derivative of the formula (I) and the sunscreen agent defined above, and a component (B) containing a retinoid in a physiologically acceptable medium.

The physiologically acceptable medium can be of the type defined above in relation to the composition containing the pyrimidine derivative of the formula (I) and the sunscreen agent.

The retinoid is present in the component (B) in the proportions stated above, namely preferably between 0.001 and 2% by weight, and especially between 0.01 and 0.5% by weight, relative to the total weight of the component (B).

The treatment of the scalp for the purpose of inducing and stimulating hair growth and decreasing its loss may be performed according to a process consisting, according to a first variant, in applying, in a first stage, the combination according to the invention consisting of a component (A) containing the pyrimidine derivative of the formula (I) and the agents screening out UV radiation, defined above, in a physiologically acceptable medium.

According to a second variant, a component (B) consisting of a composition containing a retinoid as defined above in a physiologically acceptable medium is applied either simultaneously, or successively, or even after an interval of time.

According to an especially preferred embodiment of the invention, the component (B) containing the retinoid is applied first and, after a contact time of one minute to 12 hours, the component (A) containing the pyrimidine derivative of formula (I) with the agent screening out UV radiation is applied.

It is also possible, according to a third especially preferred variant, to mix the components (A) and (B) at the required time immediately before use.

The application is preferably performed using doses of 0.5 to 2 cm^3 of each of the components or of the two components combined in a mixture prepared at the time of use.

The combination according to the invention, and more especially in the variant employing the component (A) and the component (B), may be packaged in the form of a multi-compartment device also known as a "kit" or outfit, the first compartment of which contains the component (A) based on the pyrimidine derivative of the formula (I) and the agent screening out UV radiation as defined above, and a component (B) containing a retinoid in a physiologically acceptable medium.

Another subject of the invention consists of a process for solubilizing a pyrimidine derivative of formula (I), as a result of the concomitant use of an agent screening out UV radiation as defined above.

The process according to the invention relates essentially to a therapeutic treatment for hair loss by acting especially on the functions and the biological mechanism at the origin of hair growth, and in particular via an action on this growth mechanism by prolonging the anagen phase.

This process according to the invention may also be applied in the context of a cosmetic treatment, inasmuch as it enables the hair to be rendered more attractive by endowing it with greater vigour and an improved appearance.

The examples which follow are intended as an illustration of the invention without, however, being limiting in nature.

EXAMPLE 1

The following composition is prepared:

Minoxidil	3.40 g
2-Hydroxy-4-methoxybenzophenone (UVINUL M 40, sold by the company GAF)	3.00 g
Propylene glycol 6.5 g/ethyl alcohol 93.5 g	qs 100.00 g

The solubility of minoxidil is increased relative to its solubility in the same medium without the sunscreen.

EXAMPLE 2

The following composition is prepared:

Minoxidil	3.30 g
2-Ethylhexyl p-dimethylaminobenzoate (ESCALOL 507, sold by the company VAN DYK)	3.00 g
Propylene glycol 6.5 g/ethyl alcohol 93.5 g	qs 100.00 g

The solubility of minoxidil is increased relative to its solubility in the same medium without the sunscreen.

EXAMPLE 3

The following composition is prepared:

Minoxidil	3.20 g
2-Ethylhexyl p-methoxycinnamate (PARSOL MCX, sold by the company GIVAUDAN)	3.00 g
Propylene glycol 6.5 g/ethyl alcohol 93.5 g	qs 100.00 g

The solubility of minoxidil is increased relative to its solubility in the same medium without a sunscreen.

EXAMPLE 4

The following composition is prepared:

Minoxidil	3.25 g
4-(1,1-Dimethylethyl)-4'-methoxydibenzoylmethane (PARSOL 1789, sold by the company GIVAUDAN)	3.00 g
Propylene glycol 6.5 g/ethyl alcohol 93.5 g	qs 100.00 g

The solubility of minoxidil is increased relative to its solubility in the same medium without a sunscreen.

EXAMPLE 5

The following components (A) and (B) are prepared and packaged as a kit:

Component (A)	
Composition of Example 1	100.00 g
Component (B)	
all-trans-Retinoic acid	0.078 g
Butylated hydroxytoluene	0.025 g
Propylene glycol 6.5 g/ethyl alcohol 93.5 g	qs 100.00 g

A mixture (A+B) in the ratio 60:40 by weight is prepared at the time of use and applied to the scalp on the basis of 1 cm^3 per application.

EXAMPLE 6

The following components (A) and (B) are prepared and packaged as a kit:

Component (A)	
Composition of Example 2	100.00 g
Component (B)	
all-trans-Retinoic acid	0.062 g
Butylated hydroxyanisole	0.020 g
Propylene glycol 6.5 g/ethyl alcohol 93.5 g	qs 100.00 g

1 cm^3 of a mixture (A+B) in equal parts by weight, prepared at the time of use, is applied to the scalp at each application.

EXAMPLE 7

The following composition is prepared:

Minoxidil	6.60 g
2-Ethylhexyl p-methoxycinnamate (PARSOL MCX, sold by the company GIVAUDAN)	3.00 g
Ethyl alcohol 75 g/water 25 g	qs 100.00 g

The solubility of minoxidil is increased relative to its solubility in the same medium without a sunscreen.

EXAMPLE 8

The following composition is prepared:

Minoxidil	6.10 g
N-(2-Ethylhexyl)-3-[(3'-methoxy-4'-n-butoxy)benzylidene]-10-camphor-sulphonamide	1.00 g
Ethyl alcohol 75 g/water 25 g	qs 100.00 g

The solubility of minoxidil is increased relative to its solubility in the same medium without a sunscreen.

EXAMPLE 9

The following composition is prepared:

Minoxidil	6.20 g
Homomenthyl salicylate	2.00 g
Ethyl alcohol 75 g/water 25 g	qs 100.00 g

The solubility of minoxidil is increased relative to its solubility in the same medium without a sunscreen.

EXAMPLE 10

The following composition is prepared:

Minoxidil	6.10 g
2-Ethylhexyl salicylate	2.00 g
Ethyl alcohol 75 g/water 25 g	qs 100.00 g

The solubility of minoxidil is increased relative to its solubility in the same medium without a sunscreen.

EXAMPLE 11

The following composition is prepared:

Minoxidil	4.10 g
2-Hydroxy-4-methoxybenzophenone-5-sulphonic acid	2.00 g
Ethyl alcohol 40.5 g/water 59.5 g	qs 100.00 g

The solubility of minoxidil is increased relative to its solubility in the same medium without a sunscreen.

The compositions of Example 8 to 11 are applied to the alopecic areas of the scalp having a surface area of 100 to 200 cm^3 on the basis of 2 ml per day for 3 months.

EXAMPLE 12

The following composition is prepared:

Minoxidil	3.10 g
p-Aminobenzoic acid	2.30 g
Ethyl alcohol 40.5 g/water 59.5 g	qs 100.00 g

The solubility of minoxidil is increased relative to its solubility in the same medium without a sunscreen.

EXAMPLE 13

The following composition is prepared:

Minoxidil	6.30 g
Pentyl p-dimethylamino benzoate	3.00 g
Ethyl alcohol 75 g/water 25 g	qs 100.00 g

The solubility of minoxidil is increased relative to its solubility in the same medium without a sunscreen.

EXAMPLE 14

The following composition is prepared:

Minoxidil	5.80 g
3-(4-Methylbenzylidene)camphor	3.00 g
Ethyl alcohol 75 g/water 25 g	qs 100.00 g

The solubility of minoxidil is increased relative to its solubility in the same medium without a sunscreen.

EXAMPLE 15

The components (A) and (B) are prepared and packaged as a kit:

Component (A)	
Minoxidil	4.70 g
N-(2-Ethylhexyl)-3-[(3'-methoxy-4'-n-butoxy)benzylidene]-10-camphorsulphonamide	0.30 g
Ethyl alcohol 75 g/water 25 g	qs 100.00 g
Component (B)	
all-trans-Retinoic acid	0.031 g
Butylated hydroxyanisole	0.010 g
Propylene glycol 6.5 g/ethyl alcohol 93.5 g	qs 100.00 g

The two compositions (A) and (B) are applied to an alopecic area of the scalp, separately or separated by an interval of time, either one after the other, (A) in the morning and (B) in the evening, or vice versa, or at an interval of time from 5 minutes to a few hours.

EXAMPLE 16

The components (A) and (B) are prepared and packaged as a kit:

Component (A)	
Minoxidil	4.70 g
Homomenthyl salicylate	0.50 g
Ethyl alcohol 75 g/water 25 g	qs 100.00 g
Component (B)	
all-trans-Retinoic acid	0.031 g
Butylated hydroxyanisole	0.010 g
Propylene glycol 6.5 g/ethyl alcohol 93.5 g	qs 100.00 g

The two compositions (A) and (B) are applied to an alopecic area of the scalp, separately or separated by an interval of time, either one after the other, (A) in the morning and (B) in the evening, or vice versa, or at an interval of time from 5 minutes to a few hours.

EXAMPLE 17

The following two compositions (A) and (B) are packaged as a kit:

Component (A)	
Minoxidil	3.00 g
2-Hydroxy-4-methoxybenzophenone-5-sulphonic acid	1.00 g
Ethyl alcohol 40.5 g/water 59.5 g	qs 100.00 g
Component (B)	
all-trans-Retinoic acid	0.031 g
Butylated hydroxytoluene	0.0125 g
Propylene glycol 6.5 g/ethyl alcohol 93.5 g	qs 100.00 g

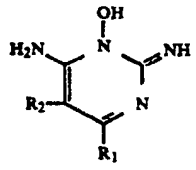
The two compositions (A) and (B) are applied to an alopecic area of the scalp, separately or separated by an interval of time, either one after the other, (A) in the morning and (B) in the evening, or vice versa, or at an interval of time from 5 minutes to a few hours.

For the different composition of Examples 1 to 17, virtually no crystallization of minoxidil on the scalp is noted.

We claim:

1. A composition for inducing and stimulating hair growth and for decreasing hair loss, said composition comprising, in a physiologically acceptable aqueous or anhydrous medium:

(a) at least an effective concentration of at least one pyrimidine derivative having the formula:

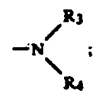


(I)

or of an acid addition salt thereof with a physiologically acceptable acid; and

(b) a sufficient concentration of at least one compound or mixture of compounds that screens out ultraviolet (UV) radiation to increase the solubility of said pyrimidine derivative in said medium compared to the solubility of the pyrimidine in the same medium in the absence of said compound or mixture of compounds that screens out UV radiation, wherein:

R_1 is a group having the formula



R_3 and R_4 are either selected from the group consisting of hydrogen, lower alkyl, alkenyl, alkylaryl and cycloalkyl, in which the alkyl portions are lower alkyl, or R_3 and R_4 with the nitrogen to which they are each bound form a heterocyclic group, which is unsubstituted or is substituted on the carbon atoms with one to three lower alkyl, hydroxy, or alkoxy groups, and which is selected from the group consisting of aziridinyl, azetidinyl, pyrrolidinyl, piperidino, hexahydroazepinyl, heptamethyleniminio, octamethyleneimino, morpholino and 4-(lower alkyl) piperazinyl;

R_2 is selected from the group consisting of hydrogen, lower alkyl, alkenyl, alkoxyalkyl, cycloalkyl, aryl, alkylaryl, arylalkyl, alkylarylalkyl, alkoxyarylalkyl and haloarylalkyl, in which the alkyl portions are lower alkyl radicals; and

said effective concentration of pyrimidine derivative is effective for inducing and stimulating the growth of hair and reducing its loss;

said UV screening compound is selected from the group consisting of 2-hydroxy-4-methoxybenzophenone, 2-ethylhexyl paradimethylaminobenzoate, pentyl para-dimethylaminobenzoate, 2-ethylhexyl para-methoxycinnamate, 4-(1,1-dimethylethyl)-4'-methoxydibenzolymethane, N-(2-ethylhexyl)-3-[(3'-methoxy-4'-n-butoxy)benzylidene]-10-camphorsulphonamide, 3-(4-methylbenzylidene)camphor, homomenthyl salicylate, 2-ethylhexyl salicylate, para-aminobenzoic acid and 2-hydroxy-4-methoxybenzophenone-5-sulphonic acid;

said aqueous medium consists essentially of water or a mixture of water and a physiologically acceptable solvent; and

said anhydrous medium is a physiologically acceptable solvent or mixture of solvents that contains less than 1% water.

2. A process for cosmetically treating the hair, comprising applying an effective amount of at least one combination of claim 10 to the scalp, wherein said amount is effective for cosmetically improving the appearance of the hair.

3. A process for therapeutically treating alopecia, comprising applying an effective amount of the composition of claim 22 to the hair for treating said alopecia.

4. A process for therapeutically treating alopecia, comprising applying an effective amount of the combination of claim 10 to the hair for treating said alopecia.

5. The composition of claim 1, wherein the concentration of the pyrimidine derivative is greater than the solubility limit of said pyrimidine derivative in said medium in the absence of said compound or mixture of compounds that screens out UV radiation.

6. The composition of claim 1, wherein the UV screening compound is 4-(1,1-dimethylethyl)-4'-methoxydibenzoylmethane.

7. The composition of claim 1, wherein R_2 is hydrogen and R_1 is a

piperidyl ring.

8. The composition of claim 1, wherein the concentration of the pyrimidine derivative of formula (I) is between 0.1 and 10% by weight relative to the total weight of the composition.

9. The composition of claim 1, wherein said sufficient concentration is between 0.1 and 10% by weight relative to the total weight of the composition.

10. The composition of claim 1, wherein said medium is an anhydrous medium.

11. The composition of claim 10 wherein said medium contains a solvent or mixture of solvents selected from the group consisting of C_2–C_4 lower alcohols, alkylene glycols and alkylene glycol or dialkylene glycol alkyl ethers.

12. The composition of claim 1, wherein said medium is an aqueous or an aqueous-alcoholic medium.

13. The composition of claim 12, wherein said medium contains water and a solvent or mixture of solvents selected from the group consisting of lower alcohols, alkylene glycols and alkylene glycol or dialkylene glycol alkyl ethers.

14. A combination that is effective for inducing and stimulating the growth of hair and reducing its loss, comprising:

(a) a composition of claim 2, and

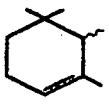
(b) a second composition containing, in a physiologically acceptable medium, an effective concentration of at least one retinoid, wherein said effective concentrations of pyrimidine derivative and retinoid are effective, when used in said combination, for inducing and stimulating the growth of hair and reducing its loss.

15. Combination according to claim 14, wherein the retinoid is selected from the compounds of formula:

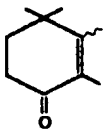
(II)

in which:

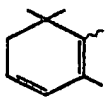
(a) A is a group selected from the groups of formulae:



(IIIa)



(IV)



(IIIb)

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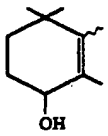
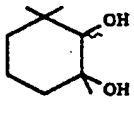


(V)



(VI)

when A denotes a group of formula (IIIa), R is selected from the following groups:

CHO; CH_2OR_5,

in which R_5 denotes hydrogen or C_1–C_4 lower alkyl;

a group

where R_6 denotes C_1–C_{16} linear or branched alkyl;

CH_2SR_7, in which R_7 denotes hydrogen or methyl;

in which X denotes:

(i) OH;

(ii) OR_8, where R_8 denotes a C_1–C_{15} alkyl radical, C_1–C_4 arylalkyl radical optionally substituted on the aryl group, C_1–C_4 arylcarboxyalkyl radical optionally substituted on the aryl group, or C_1–C_4 hydroxyalkyl or C_1–C_4 amidoalkyl radical;

(iii) NR_9R_{10}, in which R_9 and R_{10}, which may be identical or different, denote hydrogen, C_1–C_6 alkyl, C_1–C_4 hydroxyalkyl or optionally substituted aryl;

it being possible for R_9 or R_{10} to represent an optionally substituted heterocycle or, together with the nitrogen atom to which they are attached, to form a heterocycle which is itself optionally substituted;

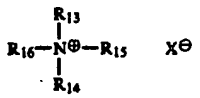
(iv) an N_3 group;

or alternatively a group of formula CH_2NHR_{11}, in which R_{11} denotes an optionally substituted benzoyl radical;

when A denotes a group of formula (IIIb), (IV), (V) or (VI), R_1 denotes COOH as well as its salified or esterified form;

b) A is a group selected from aryl or substituted aryl groups, a heterocycle or substituted heterocycle, an aryl-heterocyclic group optionally substituted on the heterocycle or an aryl-homocyclic group optionally substituted on the aromatic ring, R_1 in this case denoting a COOH group, a group $COOR_{12}$ where R_{12} denotes a C_1–C_4 alkyl radical or alternatively an amide group substituted with a C_1–C_4 alkyl group, as well as their physiologically acceptable salts and esters.

16. Combination according to claim 14, wherein the retinoid is selected from retinal, retinol, retinyl acetate, propionate and palmitate, retinoic acid in all-trans, 13-cis, 9-cis, 11-cis, 9,13-dicis and 11,13-dicis forms, the corresponding zinc retinoates and the quaternary ammonium retinoates of formula:



(VII)

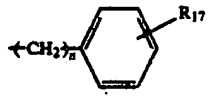
in which

$X^{\ominus}$ denotes an all-trans- or 13-cis-retinoate radical; and

(i) R_{13} R_{14} and R_{15}, which may be identical or different, denote a C_1–C_4 linear alkyl group which can bear one or more hydroxyl group(s) in the chain,

R_{16} denoting C_{12}–C_{18} linear alkenyl or alkyl;

(ii) R_{15} denotes a group:



in which:

n is equal to 0 or 1,

R_{17} represents a hydrogen or halogen atom or a hydroxyl, C_1–C_{18} alkyl or hydroxyalkyl or C_2–C_{18} acyl group;

R_{13}, R_{14} and R_{15} having the meanings stated under (i);

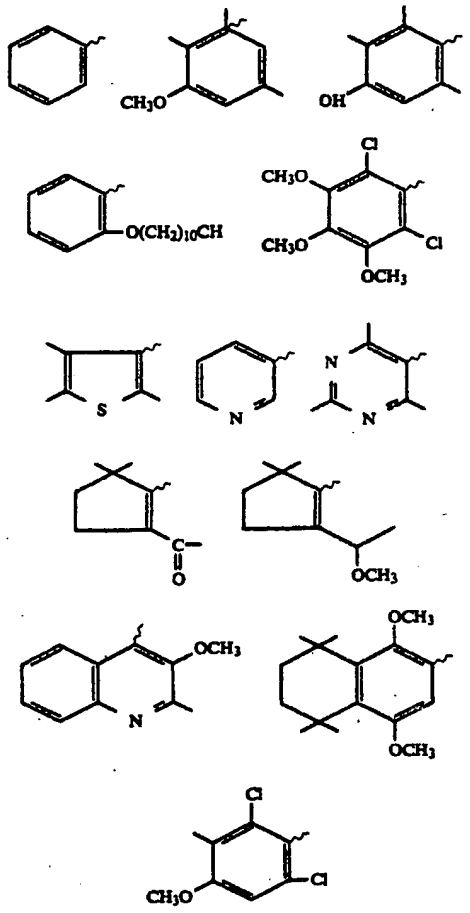
(iii) R_{13} and R_{14} can form an aliphatic heterocycle containing at least one oxygen atom, one nitrogen atom or one sulphur atom;

R_{15}or R_{16} having the meanings stated under (i) and (ii);

all-trans-retinoyloxyacetamide, a mixture of 2-hydroxy-1-propyl and 1-hydroxy-2-propyl all-trans-retinoates, 2-hydroxyethyl all-trans-retinoate, 4-nitrobenzyl all-trans-retinoate, benzyl all-trans-retinoate, 4-(all-trans-retinoyloxyacetyl)catechol, 2-cyclohexylethyl all-trans-retinoate, 10-carboxymethyldecyl all-trans-retinoate, 4-hydroxybutyl all-trans-retinoate, cholesteryl all-trans-retinoate, 4-bromobenzyl all-trans-retinoate, cholesteryl all-trans-retinoyloxyacetate, all-trans-retinoyloxyacetylbenzene, 4-(all-trans-retinoyloxyacetyl)bromobenzene, 4-(all-trans-retinoyloxyacetyl)nitrobenzene, 4-(all-trans-retinoyloxyacetyl)benzonitrile, all-trans-retinoyloxyacetyl-2,4-dichlorobenzene, N-(all-trans-retinoyloxy)phthalimide, N-(all-trans-retinoyloxy)succinimide, 4-(all-trans-retinoyloxyacetyl)methoxybenzene, 4-(all-trans-retinoyloxyacetyl)phenol, 4-(all-trans-retinoyloxyacetyl)-3,4,5-trimethoxybenzene, 4-(all-trans-retinoyloxyacetyl)-2,4,6-trimethylbenzene, 4-(all-trans-retinoyloxyacetyl)toluene, 4-(all-trans-retinoyloxyacetyl)ethoxybenzene, 4-(all-trans-retinoyloxyacetyl)acetoxybenzene, 4-(all-trans-retinoyloxyacetyl)naphthalene, 4-(all-trans-retinoyloxyacetyl)biphenyl, 4-(all-trans-retinoyloxyacetyl)-2,5-dimethoxybenzene, 1-(all-trans-retinoyloxyacetyl)-2,4-dimethylbenzene, 1-(all-trans-retinoyloxyacetyl)-3,4-diacetoxybenzene, all-trans-retinamide, 2-hydroxyethyl all-trans-retinamide, N-ethyl-all-trans-retinamide, 4-(all-trans-retinoyl-)aminophenol, N-(methyldimethyldioxolane)-retinamide, N-(ortho-carboxyphenyl)retinamide, N-(p-carboxyphenyl)retinamide, N-hydroxypropylall-trans-retinamide, N-(hydroxypropyl)-13-cis-retinamide, N-(5-tetrazolyl)-all-trans-retinamide, N-(5-tetrazolyl)-13-cis-retinamide, N-(3,4l-methylenedioxyphenylmethyl)-all-trans-retinamide, N-(n-propyl)-all-trans-retinamide, N-tert-butyl-all-trans-retinamide, N-(1,1,3,3-tetramethylbutyl)-all-trans-retinamide, N-(4-carboxymethyl-3-hydroxyphenyl)-all-trans-retinamide, N-[β-(3,4-dimethoxyphenyl)ethyl]-all-trans-retinamide, 2-(all-trans-retinoylamino)benzotriazole, 1-(all-trans-retinoyl)-1,2,4-triazole, N-(all-trans-retinoyl-)imidazole, 1-nicotinoyl-2-(all-trans-retinoyl)hydrazine, N-(all-trans-retinoyl)morpholine, trans-β-ionone (all-trans-retinoyl)hydrazone, N,N'-dicyclohexyl-N-(all-trans-retinoyl)urea, acetone (all-trans-retinoyl)hydrazone, N-benzoylretinylamine and retinoyl azide.

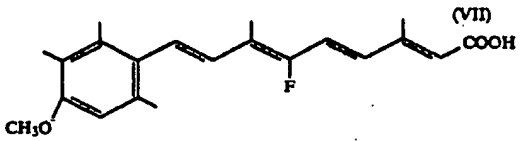
17. Combination according to claim 14, wherein retinoids correspond to formula (II) in which:

a denotes any one of the following groups:



and R denotes COOH, $CONHC_2H_5$ or $COOC_2H_5$.

18. Combination according to claim 14, wherein the retinoid is selected from the compounds of formulae:



(VII)

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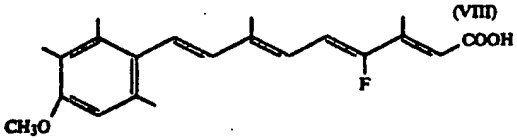
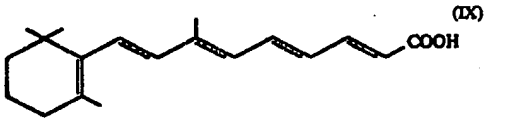
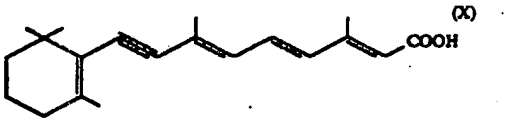
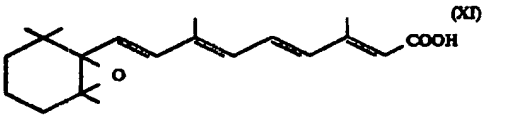
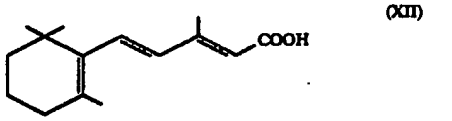








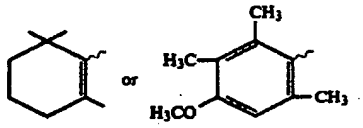


as well as their physiologically acceptable salts or esters.

19. Combination according to claim 14 wherein the retinoid is selected from the compounds of formula (II):

in all-trans or 13-cis form, in which R_1 denotes a group

where X can denote an OH group or a group OY, Y denoting an alkyl group having 1 to 15 carbon atoms, it also being possible for X to denote an amino group, optionally mono- or disubstituted with a lower alkyl group having 1 to 6 carbon atoms, R_1 also denoting a $—CH_2OH$ or —CHO group, and A denoting a group:



as well as the pharmaceutically or cosmetically acceptable salts.

20. Combination according to claim 14, wherein the retinoid is selected from tretinoin, isotretinoin, retinol or vitamin A and its derivatives such as the acetate, palmitate or propionate, motretinide, etretinate and zinc all-trans-retinoate.

21. Combination according to claim 14, wherein the components (A) and (B) form part of one and the same composition.

22. Combination according to claim 14, wherein the components (A) and (B) are intended for mixing at the required time immediately before use.

23. Combination according to claim 14, wherein the components (A) and (B) are intended for application separately or separated by an interval of time.

24. Combination according to claim 14, wherein the component (B) contains the retinoid in proportions of between 0.001 and 2% by weight relative to the total weight of the composition.

25. Multi-compartment device, comprising at least two compartments, one of which contains the component (A) and the other the component (B) as defined in claim 14.

26. A composition of claim 1, wherein said effective concentration of pyrimidine derivative is sufficient for use of said composition in the therapeutic treatment of alopecia.

27. A combination of claim 14, wherein said effective concentrations of pyrimidine derivative and retinoid are sufficient, when used in said combination, for use of said combination in the therapeutic treatment of alopecia.

28. A process for cosmetically treating the hair, comprising applying an effective amount of at least one composition of claim 1 to the scalp, wherein said amount is effective to cosmetically improve the appearance of the hair.

29. Method of treatment according to claim 28, wherein the component (B) containing the retinoid is applied in a first stage, and wherein, after a contact time of one minute to 12 hours, the component (A) containing the pyrimidine derivative of formule (I) and the agent screening out UV radiation is applied.

30. Process for cosmetic treatment of the scalp, wherein a composition resulting from a mixture of the components (A) and (B) of the combination defined in claim 14 is applied to the scalp.

31. Process for solubilizing a pyrimidine derivative corresponding to the formula (I), defined in claim 1, in a physiologically acceptable medium, wherein at least one sunscreen selected from 2-hydroxy-4-methoxybenzophenone, 2-ethylhexyl para-dimethylamino-benzoate, pentyl para-dimethylaminobenzoate, 2-ethylhexyl paramethoxycinnamate, 4-(1,1dimethylethyl)-4'-methoxy dibenzoylmethane, N-(2-ethylhexyl)-3-[(3'-methoxy-4'-n-butoxy)benzylidene]-10-camphorsulphonamide, 3-(4-methyl-benzylidene)camphor, homomenthyl and 2-ethylhexyl salicylates, para-aminobenzoic acid and 2-hydroxy-4-methoxy-benzophenone-5-sulphonic acid and 2-hydroxy-4-methoxy-benzophenone-5-sulphonic acid is added to the physiologically acceptable medium.

* * * * *

US005373012A

United States Patent [19]

Schostarez

[11] Patent Number: 5,373,012

[45] Date of Patent: Dec. 13, 1994

[54] **5-FLUORO-2,4,6-PYRIMIDINETRIAMINE COMPOUNDS**

[75] Inventor: Heinrich J. Schostarez, Portage, Mich.

[73] Assignee: The Upjohn Company, Kalamazoo, Mich.

[21] Appl. No.: 59,552

[22] Filed: May 10, 1993

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 612,695, Nov. 14, 1990, abandoned.

[51] Int. Cl.[5] A61K 31/505; A61K 31/535; C07D 403/04

[52] U.S. Cl. 514/275; 544/320; 544/322; 544/323; 544/324; 544/326; 514/256

[58] Field of Search 544/320, 322, 323, 324, 544/326; 514/275, 256

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,382,247	5/1968	Anthony et al.	544/321
3,461,461	8/1969	Anthony et al.	424/45
3,464,987	9/1969	Ursprung et al.	544/123
3,644,364	2/1972	Anthony	544/323
4,139,619	2/1979	Chidsey, III	424/45
4,287,338	9/1981	McCall	544/123
4,596,812	6/1986	Chidsey et al.	514/256
4,885,296	12/1989	Manouvy et al.	514/252

OTHER PUBLICATIONS

Chemical Abstract, 70:115172v, pp. 353–354 (1969).
Chemical Abstract, 92:128848z, p. 696 (1980).
Advanced Organic Chemistry, 3rd ed., Jerry March, John Wiley & Sons Inc., pp. 602–603 (1985).

Primary Examiner—Mukund J. Shah
Assistant Examiner—Matthew V. Grumbling
Attorney, Agent, or Firm—Donald L. Corneglio

[57] **ABSTRACT**

A 5-fluoro-minoxidil compound and compositions are disclosed which are useful in the treatment of hair growth and cardiovascular disorders. The 5-fluoro-minoxidil compounds have been shown to have increased transdermal transport than minoxidil and therefore can be used in decreased amounts to achieve the same pharmacological efficacy of minoxidil.

3 Claims, 2 Drawing Sheets

FIGURE 1

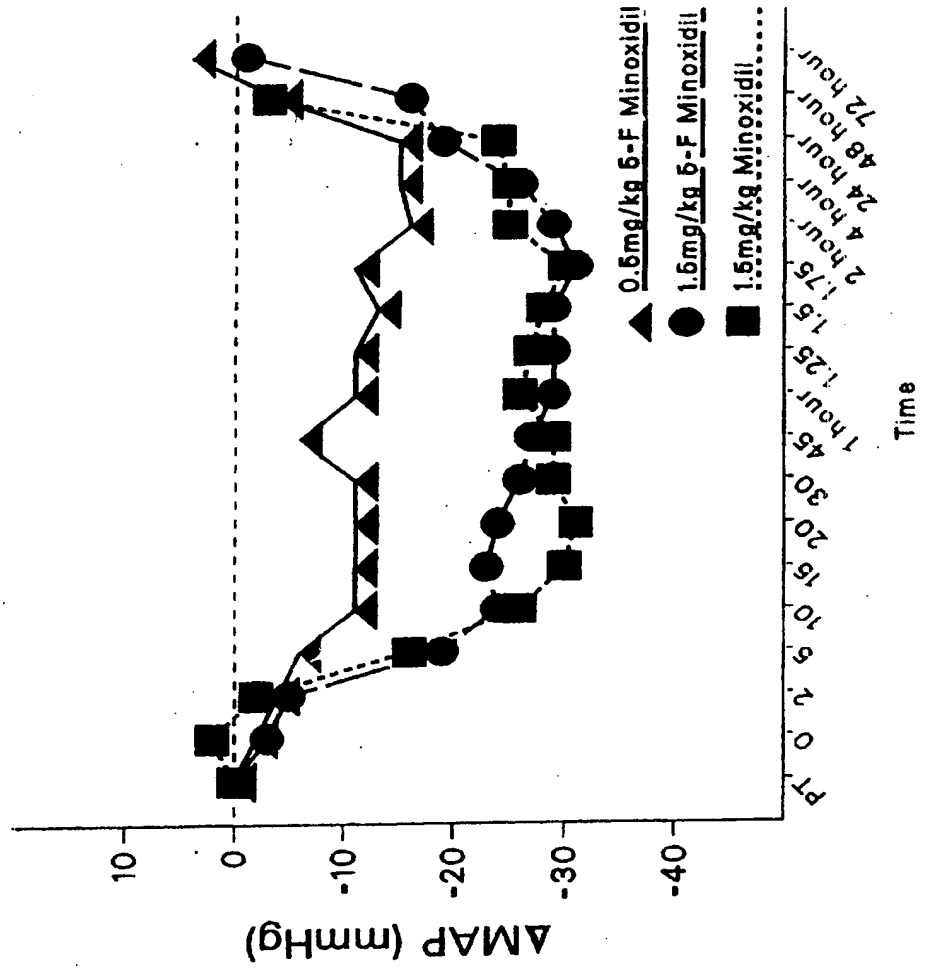
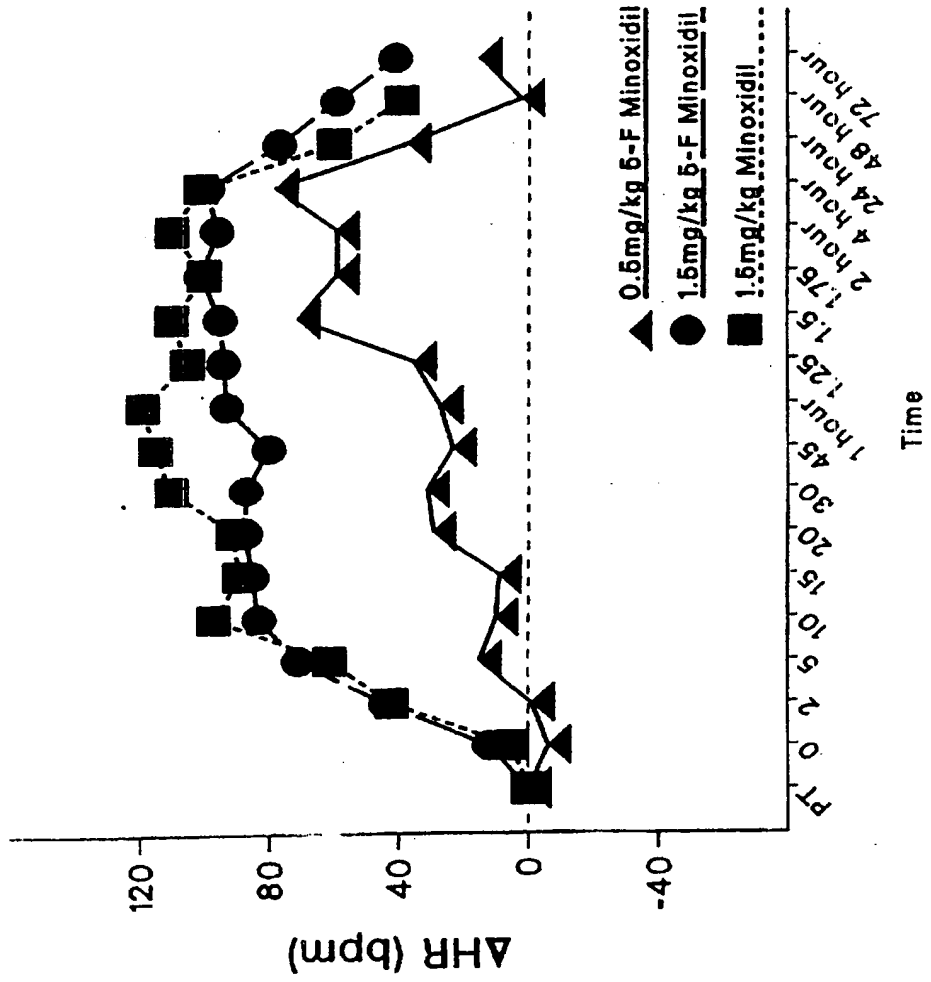

ΔMAP (mmHg)
10
0
-10
-20
-30
-40
PT
0
2
5
10
15
20
30
45
1 hour
1.25
1.5
1.75
2 hour
4 hour
24 hour
48 hour
72 hour
Time
0.5mg/kg 6-F Minoxidil
1.5mg/kg 6-F Minoxidil
1.5mg/kg Minoxidil

FIGURE 2


ΔHR (bpm)
120
80
40
0
-40
PT
0
2
5
10
15
20
30
45
1 hour
1.25
1.5
1.75
2 hour
4 hour
24 hour
48 hour
72 hour
Time
0.6mg/kg 6-F Minoxidil
1.5mg/kg 6-F Minoxidil
1.5mg/kg Minoxidil

5-FLUORO-2,4,6-PYRIMIDINETRIAMINE COMPOUNDS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of PCT/US 91/06728 (WO 92/08705), filed Sep. 20, 1991, which was a continuation-in-part of U.S. application Ser. No. 07/612,695, filed Nov. 14, 1990, abandoned.

BACKGROUND OF THE INVENTION

The present invention is directed toward a novel set of compounds, 5-fluoro-2,4,6-pyrimidinetriamines of Formula I or pharmaceutically acceptable salts thereof (hereinafter referred to as "5-fluoro minoxidil"), which are useful for the treatment of cardiovascular disorders and the promotion of hair growth. The use of minoxidil to treat cardiovascular disorders such as hypertension, congestive hear failure, and angina, peripheral vascular disorders and more recently to promote hair growth was recognized in the past and was extensively patented. Earlier patents to the minoxidil formulae itself are U.S. Pat. Nos. 3,461,461, 3,464,987 and 3,644,364 however they do not disclose or suggest a fluorine substitution even though bromine and chlorine were specifically named and in some cases iodide. Minoxidil for hair growth has also been patented in U.S. Pat. Nos. 4,139,619 and 4,596,812 however the minoxidil formulae claimed and disclosed in those patents did not show a 5-fluoro substituted minoxidil.

One explanation for this apparent deletion from the halogen family was that the fluorine atom was difficult to substitute onto the pyrimidine ring at this particular position.

The subject invention provides a method for substituting fluorine at the 5-position on a minoxidil compound and shows that this particular species has significant advantages over its halogen analogs. The 5-fluoro substituted minoxidil has bene found to have superior transdermal transport properties over unsubstituted minoxidil. The increased amount of minoxidil that is transported into the epidermis means that less can be topically applied to achieve the same hair growth pharmacological efficacy as compared to other non-fluoride substituted minoxidils. Also, because less active ingredient is used, there is significantly reduced side effects when the compound is used for hair growth.

INFORMATION DISCLOSURE

U.S. Pat. No. 4,885,296 discloses methods of preparation and compounds of 1-piperazinylpyrinidine similar to Formula I (X is O) but without the fluorine substitution.

U.S. Pat. No. 4,287,338 discloses methods of preparation and compounds of sulfooxy-pyrimidinium, -pyridinium and -triazinium similar to Formula I (X is OSO_2O) but without a fluorine substitution.

U.S. Pat. No. 3,644,364 discloses methods of preparation and compounds of 6-substituted-4-amino-1,2-dihydro-1-hydroxy-2-iminopyrimidines similar to Formula I (X is OH) but without the fluorine substitution. U.S. Pat. No. 3,464,987 discloses similar compounds with a lower alkyl substitution at the 6-position but does not disclose a fluorine substitution.

U.S. Pat. No. 3,461,461 discloses methods of preparation and compounds of 1,2-dihydro-1-hydroxypyrimidines similar to Formula I (X is OH) but without fluorine substitution.

U.S. Pat. No. 3,382,247 discloses methods of preparation and compounds of 6-amino-1,2-dihydro-1-hydroxy-2-imino-4-phenoxypyrimidines similar to Formula I (X is OH) but without a fluorine substitution.

Methods and other minoxidil compositions and compounds used for the stimulation of hair growth are disclosed in U.S. Pat. Nos. 4,139,619 (topical composition for treating alopecia) and 4,596,812 (methods for treating alopecia).

SUMMARY OF THE INVENTION

In one aspect, the present invention involves the use of a 5-fluoro minoxidil composition, Formula I, for the promotion of hair growth in mammals, especially humans. Promotion of hair growth is where the growth of hair is induced or stimulated or where the loss of hair is decreased. More specifically, any of the various analogs of the 5-fluoro minoxidil can be used for the treatment of human alopecia, including alopecia areata, androgenetic alopecia and other hair growth disorders.

The method comprises the application of an effective amount of Formula I to promote hair growth. Typically, amounts from about 0.01 to about 20, 0.1 to 10, preferably, 0.5 to 5, more preferably 1to 3 percent by weight of a compound of Formula I are applied.

The method can also comprise the application of an effective amount of such compounds admixed in a pharmaceutical carrier adapted for topical application. In another aspect the method includes the routine application of such compound to an area of treatment. Further the routine application can comprise a plurality of treatments such as, for example, daily or twice daily to promote hair growth.

In another aspect, the present invention involves the use of a 5-fluoro minoxidil composition, Formula I, for the treatment of cardiovascular disorders by parenteral, oral or transdermal administration.

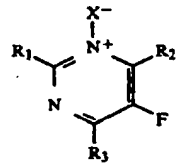
BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a chart showing changes in mean arterial pressure versus time at the doses indicated for 5-fluoro minoxidil and minoxidil.

FIG. 2 is a chart showing changes in heart rate versus time at the doses indicated for 5-fluoro minoxidil and minoxidil.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed toward novel 5-fluoro-2,4,6-pyrimidinetriamine, 1-oxide derivatives as shown in Formula I (5-fluoro minoxidil):



wherein X is O or OSO_3; R_1 is NH_2, NH—(C_1-C_5 alkyl), and NH—CO—R_4; R_2 is NH 2, CH_3, CF_3, NH—CO—R_4; R_3 is —$N(R_5)(R_6)$ wherein R_5 and R_6 are independently selected from the group consisting of hydrogen with the proviso that both are not simulta-

neously hydrogen. C_1–C_8 alkyl, C_2–C_{10} alkenyl, arylalkyl, and C_3–C_{10} cycloalkyl and the heterocyclic moieties, aziridinyl, azetidinyl, pyrrolidinyl, piperidino, hexahydroazepinyl, heptamethylenimino, octamethylenimino, morpholino, and 4-lower-alkylpiperazinyl, each of said heterocyclic moieties may have attached as substituents on their carbon atoms, zero to 3 C_1–C_5 alkyls, inclusive, a nitrogen atom of each of said heterocyclic moieties being the point of attachment of R_3 to the ring in said formula; and R_4 is O—(C_1–C_6 alkyl), CO—O—(C_1–C_6) alkyl. It is understood that C_1–C_6 alkyl includes branches and cyclic derivatives.

An "alkyl" is a straight or branched carbon chain containing the number of carbon atoms designated. An "alkenyl" is a straight or branded carbon chain having three to ten carbon atoms and containing at least one degree of unsaturation.

An "arylalkyl" is a benzyl, phenylethyl, 1-phenylethyl, 2-phenylpropyl, 4-phenylbutyl, 6-phenylhexyl, 5-phenyl-2-methylpentyl, 1-naphthylmethyl, 2-(1-napthyl)ethyl, 2-(2-napthyl)ethyl, and the like.

A "cycloalkyl" is a cyclic ring structure formed three to ten carbon atoms. The cyclic structure may also contain an alkyl substitution wherein the total carbons are calculated to include this substitution.

"Pharmacologically acceptable salts" are acid addition salts which can be prepared by any of the art recognized means. Typical, acid addition slats include hydrochloride, hydrobromide, hydroiodide, sulfate, phosphate, acetate, propionate, lactate, maleate, malate, succinate, tartrate, cyclohexanesulfamates, methanesulfonates, ethanesulfonates, benzenesulfonates, toluenesulfonates, fumarates and other pharmaceutically acceptable counter ions for amines.

This novel series of 5- fluorinated minoxidil analogues are useful in the treatment of cardiovascular disorders, such as hypertension, congestive heart failure, and angina, peripheral vascular disorders, and the treatment of alopecia, various forms such as alopecia areata, alopecia totalis, alopecia universalis and androgenetic alopecia. The subject compounds exhibit potent hypotensive activity in the dog and has exhibited activity in a in vivo hair growth rat assay. Since the subject compounds are hypotensive agents which can induce vasodilation, they can be useful as a treatment for male erectile dysfunction. Preferably the compounds are applied topically at the glans penis.

The invention also relates to compounds as described in Formula I, and combinations with antiinflammatories (steroidal and non-steroidal), androgen receptor blockers, 5α-reductase inhibitors, and β-blockers for the treatment of cardiovascular disorders, such as hypertension, congestive heart failure, and angina, peripheral vascular disorders, and the treatment of alopecia, various forms such as alopecia areata, alopecia totalis, alopecia universalis and androgenetic alopecia.

A synthesis scheme for the subject compounds is depicted on Scheme Sheet 1, below and is explained as follows:

Commercially available dimethyl fluoromalonate (1) (or the diethyl ester) is condensed with guanidine hydrochloride (2) to yield 4,6-dihydroxy-5-fluoro-2-pyrimidineamine (3). This product (3) was converted to the dichloride (4) with $POCl_3$/2-picoline. Introduction of the 4-amino group was carried out undersealed tube conditions to give (5). Oxidation of (5) with MCPBA formed the N-oxide (6) which was smoothly converted to the 5-fluoro minoxidil with piperidine in refluxing ethanol.

The compounds of the subject invention can be used for hair growth which comprises the treatment of the skin with an effective amount of Formula I, including its pharmaceutically acceptable salts whereby hair growth is promoted. The method and composition of this invention are useful for increasing hair growth over that normally experienced by the treated subject, maintaining hair growth where hair growth was previously declining or obtaining hair growth were hair growth has stopped.

Pharmaceutically acceptable salts of Formula I, are for example acid addition salts may be chosen from the following: acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, tosylate, and undecanoate.

Typically, in a hair growth application a compound of formula I is applied to the skin region where the promotion of hair growth is desired with a pharmaceutical carrier. "Promotion of hair growth" is meant to include the increase of hair growth over normal hair growth or the initiation of hair growth where hair growth has stopped prior to treatment with Formula I. More preferably, the pharmaceutical carrier is adapted for topical application such as those pharmaceutical forms which can be applied externally by direct contact with the surface to be treated.

Conventional pharmaceutical carriers or vehicles for this purpose include ointments, waxes, lotions, pastes, jellies, sprays, aerosols, and the like in aqueous or nonaqueous formulations. The term "ointment" embraces formulations (including creams) having oleaginous, absorption, water-soluble and emulsion-type bases, e.g., petrolatum, lanolin, propylene glycol, propylene carbonate, polyethylene glycols, N-methyl pyrrolidinone, oleyl alcohol, ethyl alcohol as well as mixtures of these. The use of penetration enhancers such as oleyl alcohol in concentrations of about 1% by weight may be beneficial. For example, as mixture of 84% propylene carbonate, 15% N-methylpyrrolidinone and 1% oleyl alcohol may be an effective vehicle for a hair growth promoter.

Preparation of minoxidil topical compositions are disclosed in U.S. Pat. Nos. 4,139,619 and 4,596,812, both herein incorporated by reference for their disclosure of the preparation of topical carriers as well as the preparation of a minoxidil topical preparation to which Formula I can be admixed.

Additionally, the 5-fluoro minoxidil compounds can be admixed with other compounds for the treatment of hair growth. Such compounds which can be included in the overall composition or treatment are minoxidil, pyranobenzoxadiazole, vasoconstrictors such as betamethasone dipropionate, corticosteroids such as hydrocortisone, triazines, scopolamine, antiandrogens such as cyproterone acetate, cyoctol and 5-α-reductase inhibitors such has 17β-(N-tert-butylcarbamoyl)-4-aza-5-α-androst-1-en-3-one.

Any of the above additional compounds or mixtures thereof can be admixed with a 5-fluoro minoxidil com-

pounds to form a pharmaceutically effective hair growth composition. The 5-fluoro minoxidil compound is added in an effective amount which is an amount sufficient to promote hair growth. Typically, the compound is present in an amount of from about 0.01 to about 20, from about 0.1 to about 10, from about 0.5 to about 5, or more preferably 1 to about 3 percent by weight of the composition.

The compound of formulated composition can be applied to the area to be treated, such as the scalp in humans, by spraying, dabbing or swabbing. Other less specific methods can be employed provided the active ingredient, compound of Formula I or II, is delivered to the region of a hair follicle. Preferably, the compound or formulated composition is periodically applied to the treatment area on a routine basis prior to, during and subsequent to hair growth. Generally, the routine treatment would be to apply the compound or formulated composition at least daily, preferably twice daily although more frequency applications can be used. The treated area will experience over a period of time and applications increased or stimulated hair growth or a decrease in the loss of hair.

The percentage by weight of the compound of Formula I herein utilized ranges from about 0.01% to about 20% of the pharmaceutical preparation preferably from about 0.5 to about 5% or preferably from about 1 to about 3%. In these preparations the pharmaceutical carrier for topical applications constitutes a major amount of the preparation.

The 5-fluoro minoxidil compounds were evaluated for hair growth in an in vivo hair growth assay using rats. Each rat is dosed with vehicle and drug, 200–500 microliters per day, 5 days per week. Every seven days the treated areas are shaved and the hair removed is weighed to compare normal untreated hair growth to the drug treated hair growth. After treatment of several months, the subject compositions significantly improve the condition of the hair. The results of the biological evaluation are presented in Table I.

TABLE I

Group	Hair Growth[1]	p vs Vehicle
1 mM	+0.609 ± 0.083	0.49
5 mM	+0.760 ± 0.153	0.19
25 mM	+0.952 ± 0.149	0.02
Vehicle[2]	+0.527 ± 0.081	—

[1]Presented as mean mg/in²/day.
[2]Vehicle 50/30/20: Propylene glycol/Ethanol/Water.

In Table II a direct comparison of minoxidil to a reduced amount of 5-fluoro-minoxidil was made—100 mM minoxidil to 25 mM 5-fluoro-minoxidil. This was to demonstrate the increased efficacy of the 5-fluoro-minoxidil which therefore allow a lower amount to be used to obtain similar results. The topical applied dose and vehicle was designed to provide comparable levels of transdermal delivery. The table II data shows that there is no statistical difference (p) observed when the level of hair growth stimulation of test two agents is compared.

TABLE II

Compound	Hair Growth[3]	p
Minoxidil & 100% PG[1]	+1.065	0.002
100% PG[1]	+0.487	—
5-Fluoro-minoxidil & Vehicle[2]	+0.938	0.023
Vehicle[2]	+0.528	—

[1]PG is propylene glycol.
[2]Vehicle 50/30/20: Propylene glycol/Ethanol/Water.
[3]Presented as mean mg/in²/day.

The 5-fluoro minoxidil compounds were evaluated in the macaque monkey models and show significant hair growth results.

Thirteen stumptail macaque (*Macaca specoisa*) monkeys (mixed sexes) were assigned to vehicle control and drug treated groups on the basis of baseline hair weight data.

1. Topical 50:50 vehicle (N=7)
2. Topical 100 mM U-83,868 (N=6)

The control consisted of 50% propylene glycol, 50% ethanol. The experimental composition consisted of a 100 mM concentration of topical 5-fluoro minoxidil formulated in the control vehicle. Immediately prior to the dosing phase of the study, hair was removed from a 1 inch square area (identified by four tattoos) in the center of the balding scalp. This hair collection was the baseline hair growth determination prior to the beginning of treatment. Approximately 250 μL of vehicle or 100 mM 5-fluoro minoxidil (prepared in vehicle)were topically administered to the tattooed area of the scalp. The monkeys were dosed once per day, five days per week for sixteen weeks.

At four week intervals throughout the dosing phase of the study, each monkey was shaved and the hair was collected and weighed. The body weight data (at baseline and during assay) were analyzed by the nonparametric Wilcoxon rank-sum test. Differences were significant at $p<0.05$. The hair weight data (mean±SEM) at each 4 week collection for vehicle and treatment groups were expressed as the change from baseline. Statistical analysis (ANOVA) was performed on the ranks of the data to show overall differences among groups at each 4 week collection with $p<0.10$ marginally significant, $p<0.05$ significant, and $p<0.01$ highly significant. The results after sixteen weeks of dosing is shown in Table III.

TABLE III

Group	Hair Growth (mg)[1]	p vs Vehicle
5-fluoro minoxidil	+14.8 ± 3.1	<0.01
Vehicle	−1.8 ± 2.7	—

[1]Cumulative change in hair weight from baseline.

The above data shows a statistically significant increase in the promotion of hair growth which represents a significant advancement in the art of promoting, maintaining, or restoring hair growth.

The 5-fluoro minoxidil compounds were evaluated for cardiovascular effects in an in vivo test with beagle dogs. This test procedure is described in Humprey SJ, Zins GR, *Whole Body and Regional Hemodynamic Effects of Minoxidil in the Conscious Dog*, J. Card, Pharm. 6:979-88 (1984) and in Humprey, S.J., Zins, G.R., *The Effects of Indomethacin on the Systemic and Regional Vasodilator Responses to Minoxidil in the Conscious Dog*, Chem. Path. & Pharm. 59:1 3–20 (1988). Experiments were conducted using a radiolabeled tracer microspheres technique, Wagner NH et al., *Studies of the Circulation with Radioactive Microspheres*, Invest. Radiol. 4:374–86 (1969), with conscious beagle dogs.

The results of a rapid evaluation (N=1) of the 5-fluoro minoxidil compound compared to minoxidil are presented in FIG. 1 change in Mean Arterial Pressure versus Time at the doses indicated and FIG. 2 Changes in Heart Rate versus Time at the doses indicated. At equivalent doses (1.5 mg/kg) both compounds, the 5-fluoro minoxidil and minoxidil, produce similar decreases in MAP (Mean Arterial Pressure) as well as increases in heart rate. The fluorinated analogue is at a minimum equivalent to minoxidil in this model.

The Formula I compounds are used for the treatment of cardiovascular disorders wherever a potent hypotensive drug is indicated. The compounds and compositions of Formula I are administered in a therapeutic effective amount which is an amount sufficient to control hypertension, congestive heart failure, angina and peripheral vascular disorders in the host being treated such as mammals which includes humans. Typically, the Formula I compounds are used in unit dosages of from 0.01 to 300 mg in oral or injectable preparations. Preferably, the Formula I compounds are used in unit dosages of 0.001 to 10 mg/kg for administration by routes either oral, sublingual, transdermal, or parenteral such as by subcutaneous, intramuscular, or intravenous injection.

The particular dose of compound administered according to this invention will of course be determined by the particular circumstances surrounding the case, including the compound administered, the route of administration, the particular cardiovascular disorder being treated, and similar considerations.

The Formula I compounds can be formulated into typical pharmaceutical preparations for either oral or parenteral administration. For example, the Formula I compound can be formulated into a composition by admixing with any of a number of suitable pharmaceutical diluents and carriers such as lactose, sucrose, starch powder, cellulose, calcium sulfate, sodium benzoate and the like. Such formulations can be compressed into tablets or can be encapsulated into gelation capsules for convenient oral administration.

A gelatin capsule suited to oral administration may contain, for example, a Formula I compound in the amount of about 0.1 to about 100 mg. Such formulation can be administered orally as often as needed depending upon the particular condition and patient being treated.

For parenteral administration a Formula I compound can be formulated for intramuscular or intravenous administration. In the case of treatment of a patient suffering from a severe cardiac arrhythmia, it may be desirable to administer the Formula I compound by intravenous infusion in order to effect a speedy conversion to a normal cardiac rhythm. Such normal condition can then be maintained by oral administration.

The compositions of the present invention may also include sustained release oral dosage forms and controlled release dosage forms by which the effect of the dosage is through the skin. Such compositions are those known to an ordinary skilled artisan or can be ascertained by ordinary experimentation from known compositions such as creams, gels, pastes or liquids. Typical transdermal compounds are polyethylene glycol, triacetin, propylene glycol, propylcarbonate, ethanol, water, isopropyl myristate and various mixtures thereof.

The ability of the 5-fluoro minoxidil to be absorbed in transdermal applications was measured versus minoxidil as a control. Three rats were treated with each compound for four days and on the fifth day their urine was collected over a 24 hour period. The urine was then analyzed for drug levels and converted to micrograms urine excreted per 24 hours. The compounds were administered in a 50/30/20 propylene glycol/ethanol/water vehicle. The results shown in Table IV were as follows:

TABLE IV

COMPOUND	TOTAL MICROGRAMS EXCRETED	AVERAGE
Minoxidil (Control)		
1	354	454
2	358	
3	651	
5-Fluoro Minoxidil		
1	1229	1427
2	1132	
3	1921	

The results indicate that 5-fluoro minoxidil has superior absorption over the minoxidil control.

In the following preparation of 5-fluoro minoxidil, high resolution mass spectra, infrared spectra, ultraviolet spectra, and combustion analyses were obtained on the subject compounds. High field ^{1}H-NMR spectra at 300 Mhz and ^{13}C spectra at 75 Mhz were determined on a Bruker AM-300 and chemical shifts reported as δ units relative to tetramethylsilane.

Thin-layer chromatography was conducted with Analtech 0.25 mm glass plates precoated with silica gel GF. For column chromatography. E. Merck silica gel 60, 230-400 mesh, or E. Merck prepacked Lobar columns were used. All solvents for chromatography were Burdick and Jackson or Fisher reagent grade. All nonaqueous reactions were carried out under an inert argon atmosphere unless otherwise noted.

EXAMPLE 1:
5-Fluoro-6-piperidinyl-2,4-pyrimidinediamine

A. Preparation of 5-Fluoro-4,6-dihydroxy-2-pyrimidineamine (3)

Sodium (257 mg, 11 mmol) was dissolved in absolute ethanol (50 ml) with stirring under argon. When the sodium had thoroughly dissolved, guanidine hydrochloride (2) (502 mg, 5 mmol) and diethyl fluoromalonate (1) (790 mg, 4.4 mmol) were added. The solution was left to stir at room temperature overnight. A condenser was then attached to the flask and the solution was refluxed under argon for 4.5 hours. The solution was cooled to room temperature and concentrated. The residue was redissolved in 20 ml hot H_2O and acidified to pH 4. The mixture was cooled on ice and the precipitate was collected, yielding (3) as a peach colored solid (618 mg, 96%): MS (70 eV, EI)m/z (relative intensity) 146(M+, 100), 18 (95), 172 (26), 17 (24), 300 (21); IR (mull, cm_{-1}) 3363, 1695, 1601, 1420, 1208, 677, 666; UV (MeOH, nm) 206(3,840), 235(3,380), 270(11,600). Exact Mass Calcd for $C_4H_4N_3O_2F$: 146.0366. Found: 146.0371.

B. Preparation of 5-fluoro-4,6-dichloro-2-pyrimidineamine (4)

5-Fluoro-4,6-dihydroxy-2-pyrimidineamine (3) (450 mg, 3 mmol), phosphorous oxychloride (972 mg, 6 mmol) and 2-picoline (633 mg, 7 mmol) were charged to a 15 ml round bottom flask and heated at 110° C. for 3.5 hours. The reaction mixture was then poured onto ice. The ice solution was neutralized to pH 5.5 and refluxed

under argon for 1 hour. The solution was cooled on ice and the precipitate was collected, yielding (4) as a brown solid (268 mg, 47%): MS (70 eV, EI) m/z (relative intensity) 101 (M+, 181) 183 (66), 146 (56), 85 (34), 154 (28). Exact Mass Calcd for $C_4H_2N_3Cl_2F$: 180.9610. Found: 180.9607.

C. Preparation of
5-Fluoro-6-chloro-2,4-pyrimidinediamine (5)

5-Fluoro-4,6-dichloro-2-pyrimidineamine (4) (204 mg, 1 mmol) and ammonium hydroxide (15 ml) were charged to a sealed tube and ethanol (1.5 ml) added. The tube was heated at 100° C. for 24 hours. The solution was concentrated. The residue was absorbed on silica gel and chromatographed (elution with ethyl acetate), yielding (5) as a white powder (118 mg, 65%): MS (70 eV, EI) m/z (relative intensity) 162 (M+, 100), 43 (92), 164 (33), 127 (29), 135 (16). Exact Mass Calcd for $C_4H_4N_4ClF$: 162.0108. Found: 162.0100.

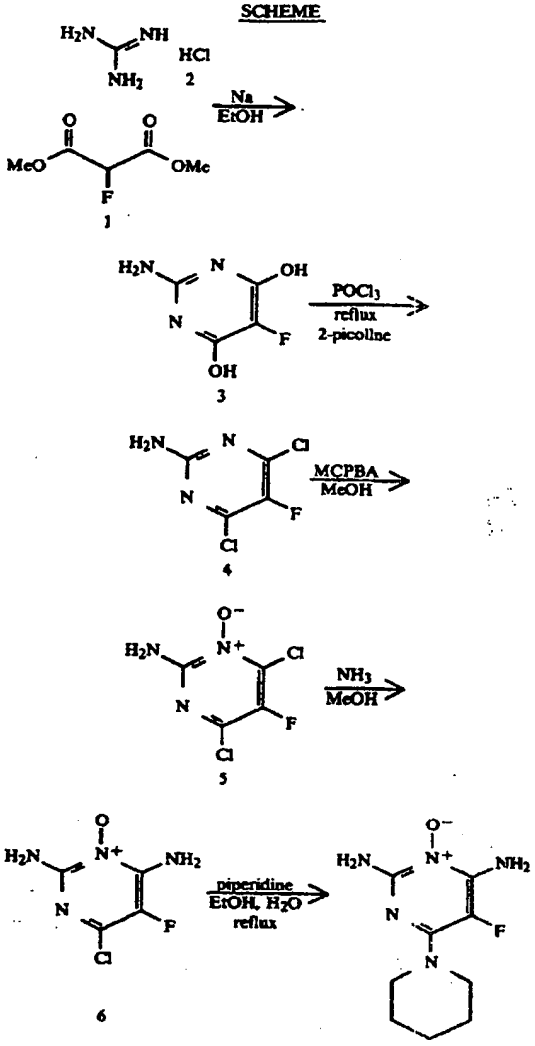
D. Preparation of
5-Fluoro-6-chloro-2,4-pyrimidinediamine, 3-oxide (6)

3-Chloroperoxybenzoic acid (303 mg, 1.4 mmol) and methanol (6 ml) were charged to a round bottom flask, which was then evacuated, flushed with argon and cooled to 0° C. After cooling, (5) (115 mg, 0.7 mmol) was added to the solution with the air of additional cold methanol (6 ml). The solution was stirred at 0° C. under argon for 5 hours and then slowly warmed to room temperature overnight. The solution was concentrated. The residue was absorbed on silica gel and chromatographed (elution with 20% methanol/chloroform+3% ammonium hydroxide), yielding (6) as a white solid (63 mg, 50%): MS (70 eV, EI)m/z (relative intensity) 178 (M+, 100), 43 (60), 180 (33), 85 (28), 44 (18). Exact Mass Calcd for $C_4H_4N_4OF$: 178.0058. Found :178.0060.

E. Preparation of
5-Fluoro-6-piperidinyl-2,4-pyrimidinediamine, 3-Oxide

5-Fluoro-6-chloro-2,4-pyrimidinediamine, 3-oxide (6) (58 mg, 0.32 mmol), piperidine (112 mg, 1.3 mmol) and 95% ethanol (2.6 ml) were charged to a round bottom flask and refluxed for 2 days. The solution was concentrated and the residue was chromatographed on silica gel (elution with 15% methanol/chloroform+2% ammonium hydroxide), yielding 5fluoro-6-piperidinyl-2,4-pyrimidinediamine 3-oxide as a white solid. (51 mg, 69%): MS (70 eV, EI)m/z (relative intensity) 84 (100), 227 (M+, 98), 210 (55), 43 (30), 40 (24); ^1H NMR (CD_3OD)δ4.91 (s, 4H), 3.61 (mult., 4H), 1.67 (mult., 2H), 1.60 (mult., 4H); ^{13}C NMR (CD_3OD) ppm 150, 147.5, 147, 123, 49.86, 27.05, 25.82. Exact Mass Calcd for $C_9H_4N_5OF$: 227.1182. Found: 227.1188.

SCHEME



I claim:

1. A compound which is 5-fluoro-6-piperidinyl-2,4-pyrimidinediamine.

2. A method for treating cardiovascular disorders in a patient in need thereof comprising the administration of a therapeutically effective amount of 5-fluoro-6-piperidinyl-2,4-pyrimidinediamine.

3. A method for promoting hair growth in a patient in need thereof comprising the topical administration of a therapeutically effective amount of 5-fluoro-6-piperidinyl-2,4-pyrimidinediamine.

* * * * *

United States Patent [19]

Zupan

[11] **4,440,777**

[45] **Apr. 3, 1984**

[54] **USE OF EUCALYPTOL FOR ENHANCING SKIN PERMEATION OF BIO-AFFECTING AGENTS**

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[52] **U.S. Cl.** ..... **424/274**; 424/45; 424/59; 424/227; 424/230; 424/238; 424/244; 424/258; 424/273 R; 424/278; 424/279; 424/310; 424/315; 424/316; 424/317

[58] **Field of Search** 424/274, 317, 278, 45

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[57] **ABSTRACT**

Greatly enhanced delivery of a wide variety of bio-affecting agents is provided by formulations for topical application comprising at least one bio-affecting agent and eucalyptol. Optionally, the formulation can further comprise a non-toxic topical carrier and/or an additional penetration enhancer. The eucalyptol acts as a unique transport agent which readily delivers the active bio-affecting agent across the stratum corneum to the target area. Cosmetic and therapeutic dermatological agents as well as systemically effective therapeutic agents can be easily formulated with eucalyptol and effectively delivered through the skin to the desired site, i.e., to the underlying tissues of the epidermis and dermis or to the general circulation.

11 Claims, No Drawings

USE OF EUCALYPTOL FOR ENHANCING SKIN PERMEATION OF BIO-AFFECTING AGENTS

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to novel compositions for topical application and delivery of a bio-affecting agent through the protective outer layer of the skin and into the underlying tissues or into the general circulation. More specifically, the invention relates to a composition comprising at least one bio-affecting agent and eucalyptol, and optionally, a nontoxic topical carrier and/or another penetration enhancer.

As used herein, the term "bio-affecting agent" refers to any chemical substance or formulation thereof which beneficially affects the mammalian body. Typically, the bio-affecting agent herein can be a "dermally effective dermatological agent" or a "systemically effective therapeutic agent". The term "dermally effective dermatological agent" as used herein refers to those chemical substances which when applied to mammalian skin exert a beneficial topical effect, which can be of a cosmetic nature (e.g., by protecting the skin against external factors or by improving appearance) or of a therapeutic nature (e.g., by attenuating the severity of a dermal disease). The term "systemically effective therapeutic agent" as used herein refers to those chemical substances which when administered by various routes such as intravenous infusion, intramuscular injection, oral, rectal or buccal routes, enter the general circulation and exhibit a therapeutic effect. The expressions "dermally effective dermatological agent" and "systemically effective therapeutic agent" are not intended to be mutually exclusive, however, it being recognized that a number of bio-affecting agents are indeed effective both dermally and systemically.

2. Description of the Prior Art

Eucalyptol is a well-known chemical compound which has long been used as an inhalational expectorant. It is also known by the names cineole and cajeputal. The art is also well-versed in the preparation of eucalyptol.

The skin of humans and other warm-blooded animals provides an excellent barrier to the penetration of exogenous chemical substances. The outer layer of the epidermis, called the stratum corneum, offers the maximum resistance to penetration, whereas the lower layers are relatively permeable. For proper treatment of dermal conditions, it is important that the active agent penetrate the stratum corneum where it is retained. From this reservoir in the outer layer, the bio-affecting agent is slowly released and penetrates the underlying areas where it exhibits its therapeutic or cosmetic effect. When dermatological agents such as sunscreens, which protect the underlying tissues from external factors (ultraviolet rays) are used, maximum retention in the stratum corneum is essential. On the other hand, the relative permeability of the layers of the epidermis below the stratum corneum can also allow access to the systemic circulation; indeed, it is necessary for the therapeutic agent to penetrate the stratum corneum in order to provide systemic therapeusis from the transdermal route.

It is well-known that the application of various therapeutic and cosmetic agents to the skin is useful for the treatment of a number of dermal conditions, e.g., hydrocortisone for pruritus and erythema in a topic dermatitis, erythromycin or tetracyclines for acne, 5-iodo-2'-deoxyuridine for herpes simplex, 5-fluorouracil for psoriasis and skin cancer, hydroquinone for lightening skin color and p-aminobenzoic acid for blocking the harmful rays of the sun.

It is also well-known that a number of therapeutically active agents, such as β-blockers, antihypertensives, antiarrhythmics, antianginal agents, vasodilators, antiemetics, antibacterials, antifungals, corticosteroids, progestins, estrogens, androgens and antiinflammatories, when administered to warm-blooded animals by a number of various routes such as by intravenous infusion, intramuscular injection, oral, rectal or buccal routes, enter the general circulation and produce the appropriate systemic therapeutic effect. It is also known that the aforementioned methods of administration have certain disadvantages. For example, the intravenous and intramuscular routes are not only painful for the patient, but also must be performed by a trained individual. Buccal and rectal administration often produce discomfort and annoyances for the patient. Oral administration, although generally acceptable for the patient, often does not deliver the majority of the therapeutic agent to systemic circulation. This diminished drug delivery is usually attributed to poor absorption from the gastrointestinal tract and/or to degradation of the agent by the acidic medium of the stomach, by the enzymes in the gastrointestinal tract and surrounding tissue or by the rapid metabolizing enzymes of the liver through which the drug must pass before it enters the systemic circulation. For example, drugs such as anti-bacterials, narcotic analgesics, β-blockers and others require relatively high doses when given orally due to the remarkable liver metabolism encountered. Effective delivery of such drugs through the skin would require much lower doses because the so-called "first pass" metabolism would be avoided.

Recognizing the fact that the outer layer of the skin, the epidermis, protects the area under the skin from the penetration of foreign chemicals, many investigators have turned to various enhancing agents, e.g., dimethylsulfoxide, dimethylformamide, methyldecylsulfoxide (U.S. Pat. No. 3,527,864) and dimethylacetamide (U.S. Pat. No. 3,472,931) in order to overcome the aforementioned problems and to deliver topically active agents more efficiently through the skin, as well as to enhance the absorption of systemically active therapeutic agents through the skin and into the general circulation. Dimethylsulfoxide, which is superior to both dimethylformamide and dimethylacetamide, has been shown to enhance the absorption through the skin of hydrocortisone and testosterone (Robert J. Feldmann and Howard I. Maibach, *Proceedings of the Joint Conference on Cosmetic Science* (1968), pages 189-203). Thus, the addition of dimethylsulfoxide to formulations of therapeutically active agents enhances the penetration of said agents through the skin and into the general circulation, thereby overcoming most of the aforementioned problems encountered by other routes of administration. Unfortunately, the use of dimethylsulfoxide is not without problems, for in addition to causing foul taste and body odor, it causes burning and erythema on the skin, activates latent virus infections within cells, reduces the relucency of the lens cortex and produces teratogenicity and tissue necrosis in animals. Compare Martindale, *The Extra Pharmacopoeia*, pages 1461-1463, Twenty-seventh Edition (1977), and the reference cited therein.

Thus, there exists a clear and present need for a novel agent to enhance the absorption through the skin of bio-affecting agents which is devoid of the disadvantages and drawbacks that to date have characterized the prior art enhancing agents.

OBJECTS AND SUMMARY OF THE INVENTION

Accordingly, a major object of the present invention is the provision of a novel agent for enhancing the skin-permeation of bio-affecting agents.

It is also a major object of the present invention to provide a novel agent which will enhance the dermal absorption of dermatological (i.e., therapeutic or cosmetic) agents and which will enhance the delivery through the skin and into the general circulation of systemically active therapeutic agents.

Another object of the invention is to provide an enhancing agent which is devoid of toxic side effects.

Yet another object of the invention is to provide novel compositions utilizing such novel enhancing agents, which formulations are useful for topical application.

Still another object of the present invention is to provide a method for enhancing the skin penetration of bio-affecting chemicals.

Other objects, features and advantages of the invention will be apparent to those skilled in the art upon a study of this disclosure and the appended claims.

It has now been unexpectedly discovered that the aforenoted objects can be achieved by employing eucalyptol as the enhancing agent and by employing same in a composition of matter further comprising at least one bio-affecting agent. The compositions can also further comprise a topical carrier material and/or an additional penetration enhancer. The bio-affecting agent is present in the composition in a biologically effective amount, i.e., in an amount sufficient to produce the desired biological effect. Thus, when the bio-affecting agent is a dermatological agent, it is utilized in a dermally effective amount, i.e., in an amount sufficient to evoke the desired dermal effect (which may be cosmetic or therapeutic in nature). On the other hand when the bio-affecting agent is a systemically active therapeutic agent and introduction of the agent into the general circulation is desired, then the agent is employed in a systemically effective amount, i.e., in an amount sufficient to produce the desired systemic response. Eucalyptol is employed in the instant compositions in an amount sufficient to enhance skin permeation of the bio-affecting agent.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides compositions and methods for surprisingly increasing the rate of penetration through the skin of various bio-affecting agents. The amount of dermatological agents absorbed into the underlying tissues of the skin and the amount of systemically effective therapeutic agents absorbed into the general circulation can be dramatically increased utilizing the compositions and methods of the instant invention.

A compositional formulation of the instant invention can simply comprise a stable solution or suspension of the bio-affecting agent in eucalyptol, or it can comprise a combination of the bio-affecting agent and eucalyptol with one or more carrier materials to form a solution, suspension, lotion, cream, ointment, aerosol spray or the like. Any suitable non-toxic or pharmaceutically acceptable topical carrier material or vehicle can be used. Such carrier materials are per se well known to those skilled in the art of topical pharmaceutical formulations. Compare, for example, *Remington's Pharmaceutical Sciences*, 14th Edition (1970). Alternatively, a solution or suspension of the bio-affecting agent and eucalyptol can be incorporated into a polymeric gel or film.

The various bio-affecting agents envisaged by the present invention are conveniently topically administered to warm-blooded animals in combination with eucalyptol in conventional unit dosage amount and form. The formulation comprised of a bio-affecting agent, eucalyptol and, if desired, vehicle(s) and/or additional penetration enhancer, can be applied directly to the skin, or can be applied to a carrier material such as a bandage, which can then be adhered to the skin.

The ratio of eucalyptol to the vehicle generally can vary from about 1:1000 to 100% eucalyptol. Additionally, however, when it is desired to use an additional penetration enhancer, a portion of either the eucalyptol or carrier can be replaced with an equivalent amount of the additional penetration enhancer. Mixtures of eucalyptol and other penetration enhancers, i.e., compounds which enhance the skin penetration of bio-affecting agents, have been found to be particularly useful in providing surprisingly excellent initial diffusion rates and extended periods of time for which such diffusion continues. For example, N,N-diethyl-m-toluamide (DEET), discussed in co-assigned and copending U.S. patent application Ser. Nos. 127,881 and 127,883, both filed Mar. 6, 1980, forms an appropriate mixture with eucalyptol. Examples of other penetration enhancers which can be used in mixture with eucalytpol include, but are not limited to, propylene glycol, N-methyl-2-pyrrolidone, isopropyl myristate and polyethylene glycol. The respective amounts of the eucalyptol and other penetration enhancers in mixture can, of course, vary depending upon the desired effects one wishes to achieve. However, it is generally preferred and convenient that about equivalent amounts, or about a 1:1 mixture of the eucalyptol and additional penetration enhancer, be used.

The concentration of the bio-affecting agent in the formulation can also vary greatly and will be dependent upon many factors, e.g., its type, bioavailability and potency, the condition for which it is administered, the surface area to which it is applied, the type of formulation used and the concentration of eucalyptol in the formulation. Such higher dosages (which may be greater by a factor of 10 to 20 times in the case of an agent such as dexamethasone) can be achieved by increasing the concentration of eucalyptol in the formulation, by increasing the concentration of the drug in the formulation, by increasing the area to which the formulation is applied, or by a combination of these measures. Generally, however, the concentration of the bio-affecting agent will vary from about 0.001% to about 80% of the total composition. The bio-affecting agent may be suspended or dissolved in the eucalyptol-vehicle comprising mixture.

The bio-affecting agents which can be formulated with eucalyptol in accordance with the instant invention are many and generally include any agent whose delivery through the protective outer layer of the skin is desired to be enhanced, e.g., dermally effective derma-

tological agents and systemically effective therapeutic agents.

Many dermally effective substances are known which can provide beneficial effects when applied topically to the skin, e.g., for the purpose of treating surface or subsurface diseases or for creating skin conditions which protect the skin from external factors. Such dermatological agents which can be made more useful by enhancing their penetration through the protection layer of the skin in accord with the present invention are exemplified by, but not limited to, the following classes of substances:

(a) Antimicrobial substances, such as antibacterial, antifungal, antiacne and antiviral agents. These substances, which can have increased percutaneous absorption when used in the present process, are illustrated by lincomycin; clindamycin; tetracycline, oxytetracycline, chlorotetracycline, and other tetracycline-type antibiotics; erythromycin; 2-thiopyridine N-oxide; halogen compounds, particularly iodine and iodine compounds such as iodine-PVP complex and diiodohydroxyquin; penicillins, such as penicillin G and penicillin V; cephalosporins, i.e. any of the many new forms of these β-lactam antibiotics such as cephalexin; any of the sulfonamide class of antibacterials; hexachlorophene; chlorhexidine; chloroamine compounds; benzoylperoxide; streptomycin or any other members of the class of aminoglycoside antibiotics; nitrofurantoin, nystatin; amphotericin B; 5-iodo-2-deoxyuridine; griseofulvin; thiabenzadole; and gramicidin. When the level of antimicrobial agents in the skin is greatly increased, the host has an improved ability to combat dermal infections such as boils, infected cuts or incisions, acne, herpes sores and ringworm.

(b) Antimetabolites, for example, 5-fluorouracil, 6-metcaptopurine, mycophenolic acid, methotrexate and the like, which have utility in the treatment of skin cancers and psoriasis.

(c) Anticholinergic agents, which are effective for the inhibition of axillary sweating and for the control of prickly heat. The antiperspirrant activity of agents such as methatropine nitrate, propantheline bromide, scopolamine, methscopolamine bromide, and the new class of soft antiperspirants, quarternary acyloxymethyl ammnonium salts [described, for example, by Bodor et al, *J. Med. chem.* 23, 474 (1980) and also in United Kingdom Specification No. 2010270, published June 27, 1979] can be greatly enhanced when formulated with eucalyptol.

(d) Steroidal antiinflammatory agents, such as hydrocortisone, hydrocortisone 17-valerate, hydrocortisone 17-butyrate, hydrocortisone 21-acetate, betamethasone valerate, triamcinolone acetonide, fluocinonide, desonide, fluocinolone acetonide, dexamethasone, dexamethasone 21-phosphate, prednisolone, prednisolone 21-phosphate, and haloprednone; as well as non-steroidal antiinflammatory agents, such as indomethacin, naproxen, fenoprofen, ibuprofen, alcolfenac, phenylbutazone, sulindac, desoxysulindac, diflunisal, aspirin and mefenamic acid. These agents are effective for treating inflammatory disorders of the skin and the underlying tissues, and the rate and extent of their penetration can be greatly enhanced by formulation with eucalyptol. Further examples of steroidal antiinflammatory agents for use in the instant compositions include cortisone acetate, hydrocortisone cyclopentylpropionate, cortodoxone, flucetonide, fludrocortisone acetate, flurandrenolone acetonide, medrysone, amcinafal, amcinafide, betamethasone, betamethasone benzoate, chloroprednisone acetate, clocortolone acetate, descinolone acetonide, desoximetasone, dichlorisone acetate, difluprednate, flucloronide, flumethasone, flumethasone pivalate, flunisolide acetate, fluocortolone, fluorometholone, fluperolone acetate, fluprednisolone, fluprednisolone valerate, meprednisone, methyl prednisolone, paramethasone acetate, prednisolamate, prednisone, prednival, triamcinolone, triamcinolone hexacetonide, cortivazol, formocortal nivazol. Additional non-steroidal antiinflammatory agents which can be formulated in combination with eucalyptol include salicylamide, salicylic acid, flufenisal, salsalate, triethanolamine salicylate, aminopyrine, antipyrine, oxyphenbutazone, apazone, cintazone, flufenamic acid, clonixeril, clonixin, meclofenamic acid, flunixin, colchicine, demecolcine, allopurinol, oxypurinol, benzydamime hydrochloride, dimefadane, indoxole, intrazole, mimbane hydrochloride, paranylene hydrochloride, tetrydamine, benzindopyrine hydrochloide, fluprofen, ibufenac, ketoprofen, naproxol, fenbufen, cinchophen, diflumidone sodium, fenamole, flutiazin, metazamide, letimide hydrochloride, nexeridine hydrochloride, octazamide, molinazole, neocinchophen, nimazole, proxazole citrate, tesicam, tesimide, tolmetin, tramadol and triflumidate.

(e) Local anesthetics, such as benzocaine, procaine, propoxycaine, dibucaine and lidocaine. Such agents are poorly absorbed through the skin but can show enhanced anesthetic properties when formulated with eucalyptol.

(f) Sunscreens, such as p-aminobenzoic acid, p-dimethylaminobenzoic acid, and their alkyl esters. These compounds are poorly retained in the skin but when formulated with eucalyptol can penetrate the stratum corneum and be better retained.

(g) Sex hormones, i.e., the estrogens, androgens and progestins, particularly the natural sex hormones estradiol, testosterone and progesterone, which are useful for a variety of cosmetic purposes such as stimulation of scalp hair growth and use in beauty preparations. Eucalyptol added to these preparations can enhance the penetration of the hormones and increase their retention.

(h) Antihistimines, such as cyproheptadine hydrochlorie (Periactin). These too can be advantageously formulated in combination with eucalyptol.

(i) Miscellaneous dermatological agents, e.g., skin lightening agents such as hydroquinone, keratolytics and agents for treating psoriasis, dermatitis, pruritis and erythema, and emollients.

A wide variety of therapeutic agents is known which can provide beneficial effects when absorbed into the systemic circulation. Formulation of such systemically effective therapeutic agents in combination with eucalyptol can greatly enhance their rate of penetration through the skin and the amount absorbed into the systemic circulation, and thus makes it possible to achieve a systemic effect through topical application of the drug. There is a significant advantage to the topical delivery of systemically effective therapeutic agents in cases where the drug is not absorbed well orally, produces gastric problems, or even if well absorbed, is rapidly metabolized in the liver immediately after absorption (the "first pass" effect). In such cases, by using topical delivery, a systemic response can be elicited at a lower dosage than required orally. At the same time, topical delivery avoids the disadvantages inherent in the intravenous route of administration, which would otherwise be necessary to achieve effective blood levels

at reasonable dosage amounts. Such systemically effective therapeutic agents which can be advantageously formulated in combination with eucalyptol are exemplified by, but not limited to, the following classes of substances:

(a) β-Blockers, such as propranolol, bupranolol, metoprolol, nadoxolol, sotalol, alprenolol, oxprenolol, carteolol, labetalol, atenolol, pindolol, timolol and timolol maleate. Because these antiarrhythmic agents are subject to extensive liver metabolism, elevated doses are required orally for clinical efficacy. Thus, formulations of eucalyptol with these agents would be especially advantageous.

(b) Antimicrobial substances, such as antibacterial, antifungal and antiviral agents. These substances, which can have increased percutaneous absorption when used in accord with the present invention, are exemplified by lincomycin; clindamycin; tetracycline, oxtetracycline, chlorotetracycline and other tetracycline-type antibiotics; erythromycin; 2-thiopyridine N-oxide; halogen compounds, especially iodine and iodine compounds; penicillins, such as penicillin G and penicillin V; cephalosporins, i.e., any of the many new forms of these β-lactam antibiotics such as cefalexin and cefoxytin; any of the sulfonamide class of antibacterials; streptomycin or any other members of the class of aminoglycoside antibiotics; nitrofurantoin; nystatin; amphotericin B; 5-iodo-2-deoxyuridine; N-formimidoyl thienamycin monohydrate; 1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinoline carboxylic acid; phosphonomycin; novabiocin; cycloserine; cephamycins, particularly cephamycin C; and griseofulvin. Eucalyptol formulations of these agents can enhance their delivery through the skin.

(c) Steroidal antiinflammatory agents, i.e., corticosteroids, such as hydrocortisone, hydrocortisone 17-valerate, hydrocortisone 17-butyrate, hydrocortisone 21-acetate, betamethasone valerate, triamcinolone acetonide, flucinonide, desonide, fluocinolone acetonide, dexamethasone, dexamethasone 21-phosphate, prednisolone, prednisolone 21-phosphate, halopredone, cortisone acetate, hydrocortisone cyclopentylpropionate, cortodoxone, flucetonide, fludrocortisone acetate, flurandrenolone acetonide, medrysone, amcinafal, amcinafide, betamethasone, betamethasone benzoate, chloroprednisone acetate, clocortolone acetate, descinolone acetonide, desoximetasone, dichlorisone acetate, difluprednate, flucloronide, flumethasone, flumethasone pivalate, flunisolide acetate, fluocortolone, fluorometholone, fluperolone acetate, fluprednisolone, fluprednisolone valerate, meprednisone, methyl prednisolone, paramethasone acetate, prednisolamate, prednisone, prednival, triamcinolone, triamcinolone hexacetonide, cortivazol, formocortal and nivazol. These compounds, which can be of great value systemically in inflammation, can be better absorbed through the skin when formulated with eucalyptol.

(d) Non-steroidal antiinflammatory agents, such as indomethacin, naproxen, fenoprofen, ibuprofen, alcolfenac, phenylbutazone, mefenamic acid, sulindac, desoxysulindac, diflunisal, aspirin, salicylamide, salicyclic acid, flufenisal, salsalate, triethanolamine salicylate, aminopyrine, antipyrine, oxyphenbutazone, apazone, cintazone, flufenamic acid, clonixeril, clonixin, meclofenamic acid, flunixin, colchicine, demecolcine, allopurinol, oxypurinol, benzydamine hydrochloride, dimefadane, indoxole, intrazole, mimbane hydrochloride, paranylene hydrochloride, tetrydamine, benzindopyrine hydrochloride, fluprofen, ibufenac, ketoprofen, naproxol, fenbufen, cinchophen, diflumidone sodium, fenamole, flutiazin, metazamide, letimide hydrochloride, nexeridine hydrochloride, octazamide, molinazole neocinchophen, nimazole, proxazole citrate, tesicam, tesimide, tolmetin, tramadol and triflumidate. These compounds are effective for treating inflammatory disorders of the skin and the underlying tissues. The rate and extent of penetration of these agents can be greatly enhanced by their formulation with eucalyptol.

(e) Antihypertensives, such as clonidine and α-methyldopa, and antiangina and vasodilator agents such as nitroglycerin, erythritol tetranitrate, isosorbide dinitrate, mannitol hexanitrate, pentaerythrityl tetranitrate, papaverine and dipyridamole. Such agents can have enhanced absorption through the skin when formulated with eucalpytol.

(f) Sex hormones, i.e., the estrogens, androgens and progestins, especially the natural sex hormones estradiol, testosterone and progesterone. These agents show very poor bioavailability by the oral route, but can be well absorbed through the skin when formulated with eucalyptol.

(g) Muscle relaxants, for example cyclobenzaprine hydrochloride and diazepam. These can be advantageously formulated in combination with eucalyptol.

(h) Antiasthma drugs, such as cromoglycic acid and its prodrugs [described, for example, in *International Journal of Pharmaceutics* 7, 63–75 (1980)]. Because of its short half-life, cromoglycic acid is an especially desirable candidate for formulation with eucalyptol according to the present invention.

(i) Antiemetics, e.g. pipamazine, chlorpromazine, and dimenhydrinate. These can also be formulated with eucalyptol in accord with the present invention.

In order to further illustrate the present invention and the advantages thereof, the following specific examples are given, it being understood that same are intended only as illustrative and in nowise limitative. In the examples, the effectiveness of eucalyptol as a penetration enhancer is illustrated by measuring the skin penetration of formulations of a number of representative bio-affecting agents with eucalyptol. Also, the skin penetration of bio-affecting agents via eucalyptol formulations were compared with that of other penetration enhancers as well as formulations of bio-affecting agents with common adjuvants. The comparisons made generally consisted of measuring the relative penetration through hairless mouse skin of the various formulations. In every case, those formulations which contained eucalyptol delivered more of the active agent through the skin than did the corresponding commercial preparation.

In the examples, skin penetration was determined using an in vitro diffusion cell procedure. The diffusion cells were obtained from Kersco Engineering Consultants, 3248 Kipling St. Palo Alto, Calif. 94306. The plexiglass diffusion cells consisted of a lower chamber with a side arm to allow sampling of the receptor phase, and a teflon lid. A teflon-coated stirring bar provided efficient mixing. The hairless mice (Jackson Labs) were sacrificed using cervical dislocation and the whole dorsal skin removed. The skin was gently stretched over the lower opening of the teflon lid and secured with a neoprene rubber gasket. The lid was then placed firmly on the lower chamber and secured with three screws. The opening in the lid left exposed an area of 8.0 cm^2 (3.2 cm in diameter) on the epidermis side through

which penetration was measured. The receptor fluid was 45 mL of buffer consisting of $1.5/10^{-1}$M NaCl, 5.0×10^{-4}M NaH_2PO_4, 2.0×10^{-4} Na_2HPO_4 and 200 ppm gentamycin sulfate adjusted to pH 7.2 with sodium hydroxide or hydrochloric acid. Air bubbles were carefully removed from the dermal surface of the skin by tipping the cell. In most cases 100 mg of formulation, solution or suspension containing the drug substance to be tested was applied evenly over the mouse skin. The cell was placed in a thermostated chamber maintained at 32±1° C. and the reservoir stirred by a magnetic stirrer 2.5 Hz. After 24 hours a sample of the receptor fluid was withdrawn by a pipet through the side arm and emptied into a test tube, capped and frozen. The concentration of applied drug in each diffusion cell sample was measured using high pressure liquid chromatography (HPLC). The results reported for each experiment are the average values from three replicate diffusion cells. Chromatography was performed on a high capability chromatograph using assay conditions specific for measurement of the target compounds in each example. Conditions are described in each example.

In the Examples which follow, percents are by weight unless otherwise specified.

EXAMPLE I

The in vitro diffusion cell method described above was used to compare the penetration of procaine in three different solutions of eucalyptol, N,N-diethyl-m-toluamide, and ethanol respectively. The solutions were made 1% in procaine and 10% eucalyptol and N,N-diethyl-m-toluamide in 90% ethanol. The straight ethanol solutions were also 1% in procaine. A 100 µl sample was applied to the hairless mouse skin. Samples were assayed by HPLC using a µBondapak RP cyano column with detection at 254 nm. The mobile phase was 800 mL water, 100 mL tetrahydrofuran, 100 mL acetonitrile and 100 µl ammonium hydroxide.

TABLE I

Amount of Procaine Diffused (µg/mL)						
	Time (Hr.)					
1% Procaine in	0.5	1	2	3	4	5
Eucalyptol/ Ethanol (1:9)	0.7	4.0	6.8	8.7	9.1	9.4
N,N—Diethyl-m-toluamide/Ethanol (1:9)	0.0	0.1	0.6	1.1	2.2	2.1
Ethanol	0.0	0.5	2.3	4.2	5.9	6.7

EXAMPLE II

The in vitro diffusion cell method described previously was used to compare the penetration of saturated suspensions of procaine in eucalyptol and N,N-diethyl-m-toluamide. The samples were prepared by adding procaine beyond the saturation point to 1 mL of solvent and equilibrating at 32°. A 100 µl sample was applied to the hairless mouse skin. Reservoir samples were analyzed by HPLC as described in Example I.

TABLE II

Amount of Procaine Diffused (µg/mL)			
	Time (Hr.)		
Procaine in	1	6	12
Eucalyptol	7	171	357
N,N—Diethyl-m-toluamide	0	30	153

EXAMPLE III

The in vitro diffusion cell method described above was used to compare the penetration of saturated suspensions of bupranolol in eucalyptol, N,N-diethyl-m-toluamide, N-methyl-2-pyrrolidone and propylene glycol. The samples were prepared by adding bupranolol beyond the saturation point to 1 mL of each solvent and equilibrating at 32°. A 100 µl sample was applied to the hairless mouse skin. Reservoir samples were analyzed by HPLC using a µBondapak RP cyano column with detection at 254 nm. The mobile phase was 60% by volume acetonitrile/40% by volume water with 2 mM ammonium dihydrogen phosphate.

TABLE III

Amount of Bupranolol Diffused (Total in mg)				
	Time (Hr.)			
Bupranolol in	1	2	4	6
Eucalyptol	1.79	3.13	4.06	4.82
N,N—Diethyl-m-toluamide	0.1	0.27	0.64	1.84
N—methyl-2-pyrrolidone	0.24	0.82	2.19	3.28
Propylene glycol	0.05	0.06	0.26	1.18

cl EXAMPLE IV

The in vitro diffusion cell method described previously was used to compare the penetration of bupranolol in eucalyptol, N,N-diethyl-m-toluamide, and a 1:1 mixture of the two solvents. The samples were prepared by adding bupranolol beyond the saturation point to 1 mL of each solvent and equilibrating at 32°. A 100 µl sample was applied to the hairless mouse skin. Reservoir samples were analyzed by HPLC as described in Example III.

TABLE IV

Amount of Bupranolol Diffused (Total in mg)					
	Time (Hr.)				
Bupranolol in	1.5	3	5.5	12	22
Eucalyptol	1.64	3.45	5.34	5.49	5.97
N,N—Diethyl-m-toluamide	0	0.13	0.64	4.29	10.70
1:1 mixture	0.65	2.16	5.38	8.35	10.77

EXAMPLE V

The in vitro diffusion cell method described previously was used to compare the penetration of saturated suspensions of indomethacin in eucalyptol, N,N-diethyl-m-toluamide (DEET), a 1:1 mixture of eucalyptol and DEET, and a 1:1 mixture of eucalyptol and polyethylene glycol. The samples were prepared by adding indomethacin beyond the saturation point to 1 mL of solvent and equilibrating at 32°. A 100 µl sample was applied to hairless mouse skin. Reservoir samples were analyzed by HPLC using a µBondapak RP cyano column with detection at 254 nm. The mobile phase was 35% by volume acetonitrile/65% by volume water with 2 mM ammonium dihydrogen phosphate.

TABLE V

Amount of Indomethacin Diffused (μg/mL)				
	Time (Hr.)			
Indomethacin in	3	6	12	24
Eucalyptol	4.8	11.0	30.3	43.6
Eucalyptol/DEET 1:1	1.8	5.0	22.6	40.5
DEET	0.1	0.5	3.5	7.1
Eucalyptol/Polyethylene Glycol 1:1	4.4	8.0	17.4	24.2

EXAMPLE VI

The in vitro diffusion cell method described previously was used to compare the penetration of indomethacin in saturated suspension in propylene glycol, N-methyl-2-pyrrolidone, a 1:1 mixture of eucalyptol and propylene glycol and a 1:1 mixture of eucalyptol and N-methyl-2-pyrrolidone. Conditions used were identical to those described in Example V.

TABLE VI

Amount of Indomethacin Diffused (μg/mL)			
	Time (Hr.)		
Indomethacin in	2	4	24
Propylene Glycol	0.13	0.31	3.5
Eucalyptol/Propylene Glycol 1:1	5.0	7.5	23.6
N—Methyl-2-pyrrolidone	0.29	0.86	12.0
Eucalyptol/N—Methyl-2-pyrrolidone 1:1	6.0	4.9	27.9

EXAMPLE VII

The penetration of dibucaine was compared in saturated suspensions of eucalyptol, a 1:1 mixture of eucalyptol and DEET, isopropyl myristate and a 1:1 mixture of eucalyptol and isopropyl myristate using the previously described diffusion cell method. Samples were prepared as described in Example V and 100 μl applied to hairless mouse skin. Reservoir samples were analyzed by HPLC using a μBondapak RP cyano column with detection at 254 nm. The mobile phase was 50% by volume acetonitrile/50% by volume water with 2 mM ammonium dihydrogen phosphate.

TABLE VII

Amount of Dibucaine Diffused (μg/mL)					
	Time (Hr.)				
Dibucaine in	2.5	4	6	12	24
Eucalyptol/DEET 1:1	3.1	9.1	12.5	35.7	71.2
Eucalyptol	11.0	28.7	36.4	69.1	110.1
Isopropyl Myristate	21.7	55.1	65.2	124.3	151.0
Eucalyptol/Isopropyl Myristate 1:1	35.3	61.8	72.9	127.6	177.8

EXAMPLE VIII

The penetration of dibucaine was examined as in Example VIII for saturated suspensions of dibucaine in eucalyptol, propylene glycol, a 1:1 mixture of eucalyptol and DEET, and eucalyptol wherein the set of cells was occluded with Teflon ® discs.

TABLE VIII

Amount of Dibucaine Diffused (μg/mL)				
	Time (Hr.)			
Dibucaine in	3	6	12	24
Eucalyptol	20.6	37.2	69.2	102.4
Eucalyptol (occluded)	23.2	47.9	108.7	170.0

TABLE VIII-continued

Amount of Dibucaine Diffused (μg/mL)				
	Time (Hr.)			
Dibucaine in	3	6	12	24
Eucalyptol/DEET 1:1	8.1	17.4	42.3	85.8
Propylene Glycol	2.3	7.4	26.8	44.4

EXAMPLE IX

The diffusion of dibucaine was examined as described in Example V for saturated suspensions of the dibucaine in N-methyl-2-pyrrolidone, a 1:1 mixture of eucalyptol and N-methyl-2-pyrrolidone, propylene glycol and polyethylene glycol respectively.

TABLE IX

Amount of Dibucaine Diffused (μg/mL)					
	Time (Hr.)				
Dibucaine in	2.5	4	6	12	24
N—Methyl-2-pyrrolidone	4.0	8.3	13.3	36.3	73.0
Eucalyptol/N—methyl-2-pyrrolidone 1:1	8.7	18.7	25.7	62.7	104.3
Eucalyptol/propylene glycol 1:1	7.5	19.0	24.7	82.3	117.0
Eucalyptol/polyethylene glycol 400 1:1	6.0	12.0	16.0	41.0	89.3

EXAMPLE X

The in vitro diffusion cell method described previously was used to compare the penetration of benzocaine via saturated suspensions of isopropyl myristate and 1:1 mixtures of eucalyptol and isopropyl myristate, polyethylene glycol and propylene glycol. Samples were prepared as described in previous examples and 100 μl samples were applied to hairless mouse skin. Reservoir samples were analyzed by HPLC using a μBondapak RP cyano column with detection at 254 nm. The mobile phase was 25% by volume tetrahydrofuran/75% by volume water.

TABLE X

Amount of Benzocaine Diffused (μg/mL)					
	Time (Hr.)				
Benzocaine in	2	4	6	12	24
Isopropyl Myristate	30.0	126.7	156.7	316.7	376.7
Eucalyptol/Isopropyl Myristate 1:1	33.3	133.3	163.3	343.3	450.0
Eucalyptol/Polyethylene glycol 400 1:1	40.0	143.3	220.0	430.0	620.0
Eucalyptol/Propylene glycol 1:1	26.7	160.0	213.3	306.7	400.0

EXAMPLE XI

The diffusion of benzocaine was examined as in Example X for saturated suspensions of benzocaine in eucalyptol, propylene glycol, a 1:1 mixture of eucalyptol and DEET, and eucalyptol wherein the set of cells was occluded with Teflon ® discs.

TABLE XI

Amount of Benzocaine Diffused (μg/mL)					
	Time (Hr.)				
Benzocaine in	2	4	6	12	24
Eucalyptol	100.0	103.3	106.7	110.0	123.3
Eucalyptol (occluded)	86.7	140.0	233.3	416.7	486.7

TABLE XI-continued

Benzocaine in	Amount of Benzocaine Diffused (μg/mL) Time (Hr.) 2	4	6	12	24
Eucalyptol/DEET 1:1	42.2	26.7	36.7	66.7	140.0
Propylene glycol	16.7	36.7	60.0	143.3	193.3

EXAMPLE XII

The previously described in vitro diffusion cell method was used to compare the penetrations of bupranolol octyl sulfate, a lipophilic salt of the beta-blocker bupranolol. Saturated solutions of bupranolol octyl sulfate in polyethylene glycol 400 and a 1:1 mixture of eucalyptol and polyethylene glycol 400 were used. The procedure of Example III was followed.

TABLE XII

Bupranolol octyl sulfate in	Amount of Bupranolol diffused (μg/mL) Time (Hr.) 3	6	24
Polyethylene Glycol 400	0.05	0.10	1.50
Eucalyptol/Polyethylene glycol 400 1:1	2.40	17.80	135.3

While the invention has been described in terms of various preferred embodiments, the skilled artisan will appreciate that various modifications, substitutions, omissions, and changes may be made without departing from the spirit thereof. Accordingly, it is intended that the scope of the present invention be limited solely by the scope of the following claims.

What I claim is:

1. A composition of matter for topical application comprising from 0.001% to about 80% of the total composition of a systemically or dermally effective non-steroidal anti-inflammatory agent selected from the group consisting of indomethacin, naproxen, fenoprofen, ibuprofen, sulindac and desoxysulindac and a skin permeation enhancing amount of eucalyptol.

2. A composition as defined by claim 1 further comprising a non-toxic topical carrier.

3. A composition as defined by claim 2 wherein the concentration of the eucalyptol is at least 0.1% of the carrier.

4. A composition as defined by claim 1 wherein said bio-affecting agent is indomethacin.

5. A composition as defined by claim 1, wherein said bio-affecting agent is ibuprofen.

6. A composition of matter as defined by claim 2, formulated as a solution, suspension, lotion, cream, ointment or aerosol spray.

7. A composition as defined by claim 1, further comprising a penetration enhancer in mixture with the eucalyptol.

8. A composition as defined by claim 7, wherein the penetration enhancer is selected from the group consisting of N,N-diethyl-m-toluamide, polyethylene glycol, propylene glycol, N-methyl-2-pyrrolidone and isopropyl myristate.

9. A composition as defined by claim 7, comprising a mixture of N-N-diethyl-m-toluamide and eucalyptol.

10. A composition as defined by claim 7, 8 or 9, wherein said mixture is a 1:1 mixture.

11. A method for eliciting a dermatological or systemic therapeutic response in a mammal which comprises topically administering thereto a dermally effective or systemically effective amount of a composition as defined by claim 1.

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